

REVIEW
QUESTIONS
GOLDMAN-CECIL MEDICINE
25TH EDITION
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Ch / 3 CARE OF DYING PATIENTS AND THEIR FAMILIES

1. A 75-year-old man with lung cancer is admitted to the hospital with severe shortness of breath. Work-up reveals no other cause of his shortness of breath other than lymphogenic spread of his cancer. His oxygen saturation is 94%. Which of the following treatments should be instituted for his dyspnea?
- A. Morphine
 - B. Benzodiazepines
 - C. Oxygen
 - D. A and C
 - E. All the above

Answer: A In randomized controlled data, opioids have been shown to decrease dyspnea both in lung cancer patients and in patients with COPD. Oxygen is helpful only if the patient has hypoxia. Benzodiazepines have not been shown to decrease breathlessness.

2. Which of the following is NOT required for a patient to be in hospice?
- A. The patient must be DNR.
 - B. The patient must have a life-limiting illness, which is likely to cause her death in 6 months.
 - C. The patient wishes to focus on quality of life rather than longevity of life.
 - D. If the patient lives at home, she must have a primary caregiver.

Answer: A The patient does not have to be DNR to be in hospice. The others are requirements of hospice.

3. Which of the following is true of depression in life-limiting illnesses?
- A. It is a normal reaction when people have a life-limiting illness, and it should not be treated.
 - B. It cannot be improved because the treatments take too long to work in patients with serious illness.
 - C. Treatment of depression decreases both morbidity and mortality.
 - D. It requires a psychiatric consult because treatment is very complicated.

Answer: C Data show that the treatment of depression improves both quality of life and mortality.

4. Which of the following is true?
- A. Telling patients that they have a terminal illness will result in their losing hope.
 - B. Telling patients they have a terminal illness has no impact on their desire for future treatment.
 - C. Telling patients that they have terminal illnesses is associated with their choosing hospice more frequently.
 - D. Patients have clearly stated that they do not want to be told that they have a terminal illness

Answer: C Data suggest that telling patients that they have a life-limiting illness is associated with a lower likelihood of choosing aggressive care at the end of life and is not associated with poorer psychiatric outcomes.

Ch / 4 CULTURAL CONTEXT OF MEDICINE

1. What percentage of immigrants to the United States have limited English proficiency?

- A. 20%
- B. 30%
- C. 40%
- D. 50%
- E. 60%

Answer: D The 2010 Census found that one in two immigrants have limited English proficiency. (Grieco EM, Acosta YD, de la Cruz GP, et al. The foreign born population in the United States: 2010. Washington, DC: U.S. Department of Commerce, 2012.)

2. A 19-year-old Vietnamese man presents for a routine physical examination. He is a recent immigrant, has no symptoms or significant medical history, and has not previously had a physical examination or any blood testing in the United States. Which of the following blood tests should you perform?

- A. HIV
- B. Hepatitis B
- C. Glucose
- D. Cholesterol
- E. All of the above

Answer: B More than half of the Americans who have chronic hepatitis B infection are Asians or Pacific Islanders. Therefore, all immigrants from Asia should be tested for hepatitis B. (Pollack H, Wang S, Wyatt Le, et al. A comprehensive screening and treatment model for reducing disparities in hepatitis B. *Health Aff.* 2011;30:1974-1983.)

3. Which of the following statements about health insurance is incorrect?

- A. Whites are more likely to have insurance than American Indians/ Alaska Natives.
- B. Latinos are less likely to have insurance than non-Latino whites.
- C. Gay/lesbian/homosexual individuals are less likely to have insurance than heterosexual individuals.
- D. Citizens are more likely to have insurance than noncitizens.
- E. Individuals who are proficient in English are more likely to have insurance than individuals who are not.

Answer: C The California Health Interview Survey provides information about health insurance coverage among population subgroups and shows differences by race/ethnicity, citizenship status, and level of English proficiency but not by sexual orientation. (University of California Los Angeles. Ask CHIS 2009, <http://www.chis.ucla.edu>. Accessed March 22, 2014.)

4. Which of the following are core community health worker functions?

- A. Cultural mediation
- B. Health education
- C. Informal counseling
- D. Social support
- E. All of the above

Answer: E Cultural mediation, health education, informal counseling, and social support are all core community health worker functions. (Brownstein JN, Hirsch GR, Rosenthal EL, Rush CH. Community health workers 101 for primary care providers and other stakeholders in health care systems. *J Ambul Care Manage.* 2011;34:210-220.)

5. Your practice has recently started seeing a large number of Hispanic immigrant patients with limited English proficiency. You have decided to make some changes to your practice to accommodate the specific needs of these patients. Which of the following approaches are appropriate?

- A. Hire Hispanic staff
- B. Ask limited English proficiency patients to bring a family member with them to provide
- C. Medical interpretation
- D. Provide cultural competency training to providers
- E. A and C
- F. All of the above

Answer: D Clinical practices can address health disparities in multiple ways, including by hiring staff who are representative of the practice population, providing professional interpreter services, offering cultural competency training to providers, and providing linguistically appropriate patient education materials. Family members should not be asked to provide medical interpretation. (Washington DL, Bowles J, Saha S. Transforming clinical practice to eliminate racial-ethnic disparities in healthcare. *J Gen Intern Med.* 2008;23:685-691.)

Ch / 5 SOCIOECONOMIC ISSUES IN MEDICINE

1. Preventing premature mortality is a prime goal for all clinicians. Of the following statements regarding premature mortality, which one is incorrect?
 - A. About 10% of premature deaths could be prevented by assuring high-quality medical care to all.
 - B. Among the various general causes of premature deaths, behavioral factors such as risky sexual behavior, alcohol and drug abuse, smoking, and obesity and physical inactivity are the most important and also offer opportunities for remediation.
 - C. Among behavioral factors, the most important cause of premature death is smoking cigarettes.
 - D. As smoking prevalence gradually decreases, the remaining smokers are smoking more cigarettes per day.
 - E. Based on current trends, obesity and physical inactivity will likely become more important causes of premature deaths.

Answer: D Statement A is correct. As important as good medical care is, the lack of such services only accounts for about 10% of premature deaths. Statements B, C, and E are correct. As regards statement D, at the same time as overall smoking prevalence has declined, the number of daily cigarettes consumed by those who continue to smoke has also declined. This decline is probably of function of several factors, including rising tobacco taxation that makes smoking more expensive, the spread of clean indoor air laws, and the increasing stigma attached to smoking.

2. Increasing evidence points to the important health impacts of social economic status (SES). Which one of the following statements regarding health and social class is correct?
 - A. Among the various components of SES, racial and ethnic characteristics contribute the most to health disparities.
 - B. Virtually all of the worst health among low SES populations can be explained by personal behaviors such as cigarette smoking and drug and alcohol abuse.
 - C. The relationship between SES and health is concentrated among those with low SES. In other words, for people above 400% of the poverty level, SES does not contribute to health status.
 - D. Because so many of the determinants of low SES (e.g., education, income, housing, net wealth) are outside the purview of clinicians, they should not be concerned about them.
 - E. Co-location of access to important social services—such as food stamps or disability payments—at medical sites can improve the social status of selected patients.

Answer: E Answer A is incorrect. Class, as measured by income, net wealth, educational status, and neighborhood, is the most important factor leading to health disparities. Regarding answer B, although personal behaviors such as smoking and physical activity are important, many other factors associated with low social class contribute to poor health. Regarding answer C, there is a stepwise association between SES and health, even at the higher levels of SES. For example, those in the top decile of SES enjoy better health than those in the ninth decile, even though both deciles have high SES. For answer D, it is true that clinicians would have a hard time improving these factors. Nevertheless, they should be conscious of them because they often influence treatment strategies (e.g., the ability to obtain nutritious food or to buy medications). Finally, answer E is correct. For example, convenient provision of food stamps for those with food insecurity would help stabilize diabetic patients.

3. Regarding per capita medical expenditures, population health, and access to medical care, which statement best expresses the performance of the United States versus other developed nations?
 - A. It leads the world in medical expenditures but trails badly in health outcomes and access to health care services.
 - B. It trails the world in medical expenditures, health outcomes, and access to care.
 - C. It is about in the middle for expenditures, health, and access.

- D. It leads the world in expenditures, health, and access.
- E. It leads the world in expenditures and health but lags in access.

Answer: A Answer A is correct as written. Of the three statements in answer B, only the second is correct. Of the three answers in C, none are correct. Of those in D, only the first is correct. And of those in E, only the first is correct.

4. Regarding the causes of rising medical expenditures in the United States, which answer is correct?
- A. Fee-for-service payment to physicians is no longer a major driver of cost escalation because it will soon be replaced by bundled or capitated payment.
 - B. The United States is an outlier in that it has more hospital beds per capita and a higher length of stay.
 - C. The United States is an outlier in that it features more physicians per capita.
 - D. There are multiple factors responsible for the patterns of expenditures in the United States, and it is unlikely that any one bears major responsibility for the high expenditure profile.
 - E. The threat and reality of malpractice suits, in a country with the highest number of lawyers per capita, is the major reason for high U.S. medical expenditures.

Answer: D For answer A, although there is much current talk about the imminent demise of fee-for-service payment, it remains the dominant way of paying physicians. Regarding answer B, the United States actually has fewer hospital beds per capita than other developed countries as well as a shorter length of stay. The cost of a day in the hospital, however, is far higher in the United States. Similarly, for answer C, the United States has fewer physicians per capita than most developed nations but has a much higher proportion of specialists. Answer D, the correct answer, reflects the multiple reasons that medical care is more costly in the United States. Regarding answer E, malpractice suits are indeed more of a factor in the United States than other nations. Nevertheless, if all malpractice costs were to vanish, the United States would still have the most expensive health care system by far.

5. Regarding responses to high medical expenditures in the United States, which of the following statements is most correct?
- A. Because expenditures on medical care are so essential and because wealthy countries characteristically spend more on health care as wealth increases, there is little interest in curtailing rising medical expenditures.
 - B. The cost-containment measures found in the Patient Protection and Affordable Care Act will be sufficient to rein in rising medical costs.
 - C. The combination of pressures on personal and governmental health care spending and crowding out of other social expenditures makes it likely that more intense cost-containment activity will occur.
 - D. The combination of widespread electronic medical record use and the spread of Accountable Care Organizations will be sufficient to curb rising medical expenditures.
 - E. Political obstacles to cost containment, such as the fear of rationing, will not be a problem.

Answer: C Answer A is incorrect. There is emerging consensus that something must be done to curtail rising medical expenditures (as phrased in answer C), but not on how to accomplish that. Although there are some cost-containment features in the Patient Protection and Affordable Care Act (PPACA) (answer B), it is unproved whether they will reduce medical expenditures. Answer C is correct. Regarding answer D, there is no good evidence that either the spread of electronic medical records or Accountable Care Organizations will curb rising medical expenditures, despite the enthusiasm of advocates for those programs. Finally, political obstacles (answer E) remain potent barriers to medical cost containment, such as the assertion during the debate over the PPACA that access to palliative care services would be tantamount to creating death panels.

Ch / 6 GLOBAL HEALTH

1. Based on the Global Burden of Disease Study 2010, which one of the following statements is correct?
 - A. The global burden of diabetes mellitus remained stable between 1990 and 2010.
 - B. Cancer is the leading cause of noncommunicable disease-related deaths.
 - C. Cardiovascular and circulatory deaths accounted for almost 30% of all deaths in 2010.
 - D. The total number of deaths due to HIV/AIDS and tuberculosis decreased in 2010 compared with 1990.
 - E. Forces of nature, war, and legal intervention decreased in 2010 compared with 1990.

Answer: C See Table 6-3. In 2010, the number of cardiovascular-related deaths was 15.6 million out of the total deaths of 52.8 million, amounting to 29.6%. The number of diabetes-related deaths in 1990 and 2010 were 1.5 million and 2.7 million, respectively. During those 20 years, diabetes mellitus increased by 76%. Cancer was the second leading cause of deaths in 2010. There were 8.0 million deaths due to cancer in 2010 compared with 15.6 million deaths from cardiovascular and circulatory causes. The number of deaths due to HIV/AIDS and tuberculosis in 2010 (2.7 million) increased by 50% compared with the 1990 number (1.8 million). Compared with 1990, deaths resulting from forces of nature, war, and legal intervention more than doubled (125%) by 2010.

2. Hypertension or high blood pressure is the major risk factor for heart disease, stroke, and kidney diseases worldwide. Which one of the following statements is incorrect?
 - A. The prevalence of hypertension, globally, after the age of 25 years varies between 35 and 45%.
 - B. Across all countries, men have a slightly higher prevalence of hypertension than do women.
 - C. The global hypertension control rate is about 60%.
 - D. Early diagnosis of hypertension leads to prevention of all forms of vascular complications.
 - E. According to the World Health Organization, population-attributable deaths due to hypertension are estimated at about 7.5 million per year.

Answer: C The global control rate varies from less than 5% in Zambia to 66% in Canada and is very low overall worldwide. All other statements (answers A, B, D, and E) are correct.

3. Which of the following statement about global health is correct?
 - A. Global health is not the opposite of domestic health.
 - B. Global health must integrate both infectious diseases and noncommunicable diseases.
 - C. Public, private, and societal partnership is necessary to deliver effective global health.
 - D. Academia has a major role in promoting global health.
 - E. All of the above.

Answer: E Statement A is true because global health includes domestic health as well, particularly the health of marginalized people in developed countries. Statement B is true because the current health system must address all diseases, particularly when noncommunicable diseases account for 65% of all global causes of death. New evidence shows that one fifth of all cancers worldwide are caused by chronic infections produced by agents such as HIV, human papillomavirus, and hepatitis B virus. Infections and parasitic diseases also cause other noncommunicable diseases, such as rheumatic heart disease, Chagas disease, cardiomyopathy, and peptic ulcer. As HIV/AIDS survivors live longer, they also are exposed to lifestyle-related risk factors and noncommunicable diseases. Statement C is true. The economic burden of diseases is so large that public-private partnership is essential. Statement D is true. Academia should develop and supply needed knowledge and train the next generation of the global health work force.

Ch / 7 APPROACH TO THE PATIENT: HISTORY AND PHYSICAL EXAMINATION

1. A 24-year-old-woman with right lower quadrant abdominal pain and vaginal bleeding has a positive home pregnancy. Before a pelvic ultrasound is ordered, the pelvic examination is performed and reveals cervical motion tenderness. Cervical motion tenderness has the following diagnostic characteristics for an ectopic pregnancy: sensitivity 45%, specificity 91%, likelihood ratio positive (LR+) 4.9, LR negative (LR-) 0.62, positive predictive value (PPV) 46%. Which of these values is most helpful for assessing the probability that she has an ectopic pregnancy?

- A. Sensitivity
- B. Specificity
- C. Likelihood ratio positive
- D. Likelihood ratio negative
- E. Positive predictive value

Answer: C The sensitivity is the percentage of patients who have cervical motion tenderness among women with an ectopic pregnancy. The specificity is the percentage of patients who do not have cervical motion tenderness among women without an ectopic pregnancy. These individual values are not helpful for this particular patient (Crochet JR, Bastian LA, Chireau MV. does this woman have an ectopic pregnancy? The rational clinical examination systematic review. *JAMA*. 2013;309:1722-1729) because without knowing whether or not she has an ectopic pregnancy, we do not know which result applies. The PPV describes the probability of ectopic pregnancy when there is cervical motion tenderness. To use the PPV for this patient requires knowing the prevalence of disease from which the PPV was derived. Without knowing that value, you cannot be certain whether the PPV is appropriate for your patient. The LR+ quantifies the increase in odds of disease among those with cervical motion tenderness, and the LR- quantifies the decrease in odds of disease when cervical motion tenderness is absent. Based on your assessment of the prior probability of ectopic pregnancy, which is 10 to 20% among all pregnant women with abdominal pain and/or vaginal bleeding, the LR+ is the most relevant value because it can be used to determine the increase in likelihood of ectopic pregnancy (Chapter 10).

2. The primary role of completing a review of systems in helping with clinical diagnosis during the clinical evaluation is which of the following?

- A. To review symptoms associated with the presenting problem
- B. To pick up the presence of concerns that were uncomfortable to address during the history of the present illness
- C. To complete a record that enhances patient billing
- D. To focus on the presence or absence of findings during a constrained time period
- E. To allow open-ended questioning that enhances the patient's relationship with the physician

Answer: D A complete medical history should reveal the most important symptoms experienced by the patient that are pertinent to the presenting problems. Open-ended questioning should occur during elicitation of the medical history. Although completing a review of systems may be required for electronic medical records and billing, simply fulfilling that function does not help with diagnosis. However, about 10% of the time, the review of systems might pick up on an important finding that was not addressed during the rest of the evaluation. The main purpose of the review of systems is to use direct questioning to pick up on a limited set of symptoms, during a specified recent time interval (e.g., over the past week, or the past month). This approach helps the patient focus on a well-defined and recent time period that should enhance the reliability of their answers that pertain to their current condition.

3. While conducting your new patient evaluation on a 35-year-old male veteran who served in combat duty in Afghanistan, you note that he seems anxious and that he is questioning you frequently about a variety of difficulties in making his appointment and the attitudes of your office staff. You recognize the need to screen for post-traumatic stress disorder using a four-item screening instrument. You start by asking, "In your life, have you ever had an experience so horrible, frightening, or upsetting that, in the past month you ..." All of the items below are part of the four-item screening instrument for post-traumatic stress disorder that follows this introduction except:

- A. Have little interest or pleasure in doing things?
- B. Have had nightmares about it or thought about it when you did not want to?
- C. Tried hard not to think about it or went out of your way to avoid situations that reminded you of it?
- D. Were constantly on guard, watchful, or easily startled?
- E. Felt numb or detached from others, activities, or your surroundings?

Answer: A The loss of interest or pleasure in doing things is a symptom that suggests depression. The other symptom that is elicited in a two-item screener for depression asks the patient whether they feel down, depressed, or hopeless (Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care.* 2003;41:1284-1292). Patients who answer "yes" to at least one of the items have an LR+ of 2.7 for depression, whereas answering "no" to both questions makes depression much less likely with an LR of 0.14 (Williams JW Jr, Noël P, Cordes JA, et al. Is this patient clinically depressed? *JAMA.* 2002;287:1160- 1170). Although it is important to screen for depression among patients with post-traumatic stress disorder (military related or not) (Campbell DG, Felker BL, Liu CF, et al. Prevalence of depression-PTSD comorbidity: implications for clinical practice guidelines and primary care-based interventions. *J Gen Intern Med.* 2007;22:711-718), screening for depression alone may not detect the associated post-traumatic stress disorder.

Ch / 8 APPROACH TO THE PATIENT WITH ABNORMAL VITAL SIGNS

1. A patient presents with malaise, cough, and shortness of breath. Vital signs include temperature 40° C, blood pressure 120/74 mm Hg, respiratory rate 18 breaths per minute, pulse 70 beats per minute, and oxygen saturation 97%. This presentation could be consistent with:

- A. Streptococcal pneumonia
- B. Pyelonephritis due to *Escherichia coli*
- C. Legionella pneumonia
- D. Influenza-like illness
- E. Mycoplasma pneumonia

Answer: C This patient is exhibiting a pulse-temperature dissociation because the pulse (70) is far lower than one would expect given that the patient is febrile to 40° C. This phenomenon is seen in a number of conditions, including typhoid fever and legionella infection. The other conditions would all be expected to produce tachycardia unless the patient could not become tachycardic because of medications (e.g., β -blockers) or cardiac conduction problems.

2. An 88-year-old man presents from a nursing home with slight agitation and vital signs that include temperature 38.7° C, blood pressure 96/64 mm Hg, respiratory rate 22 breaths per minute, pulse 94 beats per minute, and oxygen saturation 96%. Physical examination reveals dry mucous membranes, clear lungs, a soft abdomen, an indwelling Foley catheter, and slightly cool but noncyanotic extremities. The patient should be given:

- A. Antipyretics (e.g., acetaminophen)
- B. Intravenous normal saline, 500 mL with additional boluses as tolerated
- C. Intravenous antibiotics
- D. All of the above
- E. Only A and B until urine culture results are available

Answer: D This case is an example of how vital signs can guide treatment in the absence of a firm diagnosis. The patient meets all three of the physical examination criteria for the systemic inflammatory response syndrome (SIRS) and is likely septic. The physician should not wait for his white blood cell count or other laboratory results to initiate antibiotic treatment because evidence suggests that early antibiotics are a crucial step in preventing morbidity and mortality. Although antibiotics should not be overused, the early provision of appropriate broad-spectrum antibiotics before the confirmation of a specific diagnosis is prudent and may be life-saving for this patient.

3. An intern is awakened at 3 am by the ward nurse regarding a patient who is postoperative day 2 from a hip replacement and is newly tachycardic. Vital signs include temperature 36° C, blood pressure 146/82 mm Hg, respiratory rate 18 breaths per minute, pulse 112 beats per minute, and oxygen saturation 97% on room air. The intern drowsily orders a 1000-mL normal saline fluid challenge for dehydration. Later that morning, the patient is acutely intubated for respiratory distress. What most likely went wrong?

- A. The intern failed to consider pulmonary embolism as a possible cause for the tachycardia.
- B. The intern failed to consider fat embolism in a patient who had recently undergone hip surgery.
- C. The intern failed to consider sepsis in the differential diagnosis.
- D. The intern failed to consider failure of the patient controlled anesthesia (PCA) pump in the differential diagnosis.
- E. The intern failed to realize that tachycardia can be present in both dehydration and heart failure.

Answer: E First and foremost, the intern's main mistake was not getting out of bed to evaluate the patient in person. Vital signs alone are not sufficient data on which to base an important clinical decision. Although choices A and B are certainly possible in a postoperative orthopedic patient, heart failure is a more likely diagnosis. There is little clinical support for the other choices.

4. A patient arrives in the emergency department comatose with decreased respiratory rate in the winter. Vital signs are temperature 36° C, blood pressure 128/68 mm Hg, respiratory rate 10 breaths per minute, pulse 100 beats per minute, and oxygen saturation 100% on room air. Pupils are 6 mm and reactive, and lungs are clear. What is the single most important initial treatment?

- A. High-flow O₂ administered by non-rebreather mask
- B. Intravenous normal saline, 1000 mL with additional boluses as tolerated
- C. Intravenous antibiotics
- D. Naloxone, 0.8 mg IV
- E. Immediate endotracheal intubation

Answer: A This patient may have carbon monoxide poisoning. It is winter, a time when people use heating devices that may have incomplete combustion. The pupillary examination is not suggestive of opiate intoxication (D), and no other diagnosis is apparent. Because oxygen is the best treatment for this condition and is generally harmless in adults, it makes sense to initiate this therapy while efforts (e.g., blood gas analysis with co-oximetry) are made to confirm the diagnosis. There is no basis for thinking this patient is dehydrated (B) or infected (C), and intubation would be premature (E). Remember that pulse oximetry is falsely elevated in carbon monoxide poisoning, so the 100% oxygen saturation means nothing.

Ch / 9 STATISTICAL INTERPRETATION OF DATA

1. A study of 105 vegan Buddhist nuns randomly sampled from monasteries around Ho Chi Minh City found that the average femoral neck bone mineral density was 0.62 g/cm², with a standard deviation of 0.11 g/cm² (Ho-Pham LT, Nguyen PL, Le TT, et al. Veganism, bone mineral density, and body composition: a study in Buddhist nuns. *Osteoporos Int.* 2009;20:2087-2093). Which of the following statements about this result is correct?

- A. The 95% confidence interval for the mean bone mineral density in these women is about 0.4 to 0.84 g/cm².
- B. If bone mineral density is normally distributed, we would expect about 10% of the women in the sample to have bone mineral density outside of the interval: 0.4 to 0.84 g/cm².
- C. The 95% confidence interval for the mean bone mineral density in these women is about 0.60 to 0.64 g/cm².
- D. Because the women were sampled randomly, there is a 95% chance that a randomly selected woman from the *population* would have a bone mineral density between 0.60 and 0.64 g/cm².
- E. Because the women were sampled randomly, there is a 95% chance that a randomly selected woman from the *sample* would have a bone mineral density between 0.60 and 0.64 g/cm².

Answer: C We would expect about 95% of *observations* to be within 2 standard deviations of the sample mean, leaving 5% out, so choice B is incorrect. The 95% confidence interval for a sample mean is about mean $\pm$ 2 standard

errors of the mean (SEM), where the SEM $SD = N$. In this case, the SD is

0.11 g/cm², and the N is about 100, so the SEM will be about $0.11/10 = 0.01$ g/cm², and the 95% CI will be about 0.60 to 0.64 g/cm², as indicated in choice C. Choices D and E are incorrect because the range given is too narrow: it is $\pm$ 2 SEM when it should be $\pm$ 2 SD.

2. A study of data collected through the Get with the Guidelines-Stroke Program examined the time from onset of stroke symptoms to treatment with tissue-type plasminogen activator (tPA) among 58,353 patients with acute ischemic stroke treated within 4.5 hours of the onset of symptoms (Saver JL, Fonarow GC, Smith EE, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *JAMA.* 2013;309:2480-2488). The authors reported that “faster onset-to-treatment time, in 15-minute increments, was associated with ... increased achievement of independent ambulation at discharge (OR, 1.04; 95% CI 1.03-1.05; $P < 0.001$)” Which of the following is a correct interpretation of these findings?

- A. In this study, the effect of a 15-minute reduction in onset-to-treatment time was associated with a 4 % (relative) increase in the odds of independent ambulation at discharge.
- B. Because the odds ratio is very close to 1.0, the results are not statistically significant.
- C. Because the odds ratio is very close to 1.0, the results, although highly statistically significant, are not clinically significant.
- D. The 4% increase in odds of independent ambulation translates into a number-needed-to treat (NNT) of 25.
- E. None of the above is correct.

Answer: A Choice A exactly expresses the meaning of the odds ratio for this study. Choices B and C are incorrect because the proximity of the odds ratio to 1 is in this case based partly on the choice of the authors to express it per 15 minutes onset-to-treatment time. This illustrates the importance of knowing the units of the predictor variable when it is not dichotomous. If the authors had expressed the difference per hour instead of per 15 minutes, the odds ratios would have been taken to the fourth power, that is, the odds ratio for independent ambulation at discharge would have been about $1.044 = 1.17$. Choice D is incorrect because estimation of the NNT requires knowing the absolute risk reduction, which was not provided in this case.

3. Assume a study of both smoking and nonsmoking mothers reports that the effect of smoking on birthweight is about a 32-g decrease in birthweight per cigarette smoked per day during pregnancy (similar to what is reported by Juarez SP, Merlo J. Revisiting the effect of maternal smoking during pregnancy on offspring birthweight: a quasi-experimental sibling analysis in Sweden. *PLoS One*. 2013;8:e61734.). Which of the following statements about this finding is NOT correct?

- A. The result is based on a *model*, in which the predicted birthweight is linearly related to the number of cigarettes smoked per day.
- B. This model predicts that the difference in birthweight between a baby whose mother did not smoke and one who smoked 5 cigarettes per day is the same as the difference between babies of mothers who smoked 20 and 25 cigarettes per day.
- C. The model predicts the same effect of smoking on birthweight, regardless of the mother's age and prepregnancy weight.
- D. This model predicts that cutting cigarette smoking in half will lead to a 64-g expected weight increase in the baby.
- E. The model could include additional terms that would reflect the effect of mother's age and prepregnancy weight.

Answer: D Choices A, B and C accurately describe characteristics of a linear model for the effect of smoking on birthweight. Choice D is not consistent with a linear model. Choice E reflects that the effects of other variables can be taken into account, while still maintaining a linear model for the effect of cigarettes smoked on birthweight.

4. A case-control study of the relationship of breast cancer and the use of COX-2 inhibitors found that the odds ratio and confidence interval relating cancer to use of baby aspirin were OR = 0.77 and 95% CI (0.42-1.41) (Harris RE, Beebe-Donk J, Alshafie GA. Reduction in the risk of human breast cancer by selective cyclooxygenase-2 [COX-2] inhibitors. *BMC Cancer*. 2006;6:27). The authors then stated, "Neither acetaminophen nor baby aspirin had any effect on the relative risk of breast cancer." This is incorrect because of which of the following?

- A. The confidence interval crosses 1.
- B. The authors do not give the *P* value.
- C. The confidence interval has a lower limit of 0.42.
- D. Odds ratios are inappropriate for this study.
- E. The authors should have used a higher level of confidence.

Answer: C C is correct because the confidence interval allows for a 58% reduction (from [1 to 0.42]*100%) in the chance of breast cancer associated with the use of baby aspirin, a potentially important effect. Choice A is incorrect because it merely indicates a lack of a statistically significant result and does not bear on the size of the effect. Choice B is incorrect because CIs are more useful for ruling out important effects. Odds ratios are especially useful in case-control studies, so D is incorrect. And E is incorrect because a higher level of confidence would make the CI even wider.

5. In a randomized trial of an intervention to reduce hypertension, researchers selected subjects from a single antihypertensive patient club in Shanghai (Xue F, Yao W, Lewin RJ. A randomised trial of a 5 week, manual based, self-management programme for hypertension delivered in a cardiac patient club in Shanghai. *BMC Cardiovasc Disord*. 2008;8:10). About one third of those approached agreed to be randomized. The results of this study can be safely generalized to which of the following?

- A. All hypertensives
- B. All hypertensives in China
- C. All hypertensives in Shanghai
- D. All hypertensives belonging to the single club in Shanghai
- E. None of the above.

Answer: E Because two thirds of the participants refused to participate, the extrapolation of the effect of the intervention might not even apply to the particular club in which the study was conducted, much less a broader population.

Ch / 10 USING DATA FOR CLINICAL DECISIONS

1. A 53-year-old man presents to his primary care physician with a chief complaint of chest pain for the past 2 weeks. The pain is described as intermittent, usually exertional, midline, and aching in nature. His electrocardiogram is completely normal. Which one of the following is the most appropriate next step?

- A. Watch and wait
- B. Exercise electrocardiography
- C. B-type natriuretic peptide
- D. Exercise nuclear scintigraphy
- E. Coronary angiography

Answer: B The immediate question is whether this patient's symptoms represent new ischemic heart disease. His clinical presentation suggests a moderate probability of coronary artery disease, so watch-and-wait is probably too risky a strategy. At the same time, he does not appear to have unstable ischemic disease, so there is no need to proceed immediately to coronary angiography in preparation for coronary revascularization. Measurement of B-type natriuretic peptide would not alter management. Of the two noninvasive tests for ischemic heart disease, exercise electrocardiography is the least expensive, is the most convenient, and carries no radiation exposure. Guidelines would thus suggest that answer B is the most appropriate next step.

2. A patient undergoes an exercise test and has 2 mm of ST-segment depression on electrocardiogram. In which one of these patients would this finding be most likely to change management?

- A. A healthy 19-year-old volunteer in a research study
- B. A 62-year-old woman who is completely asymptomatic
- C. A 62-year-old woman with frequent nonexertional aching chest pain
- D. A 62-year-old woman with recent myocardial infarction and chest pain at rest
- E. A 62-year-old woman who is completely symptom free 4 months after coronary artery bypass graft surgery

Answer: C Patients A and B have a sufficiently low probability of coronary disease that the exercise test abnormality is highly likely to be a false-positive result. Patient D has an extremely high probability of coronary disease and likely needs coronary angiography and revascularization as next steps; she does not need exercise electrocardiography because the test is unlikely to change this management plan. Patient E's care is also not likely to be influenced by an exercise test result because she is asymptomatic after major coronary revascularization surgery. Patient C has a low to moderate probability of coronary disease, and this abnormal exercise test result moves her into a mid-range probability. Thus, she is likely to undergo either further testing, initiation of antianginal therapy, or both as a result of this exercise test result.

3. Which one of the following is NOT an important consideration when weighing whether to order a test for a patient?

- A. Test may influence decision making for patient's care
- B. Test is less expensive than alternative strategies
- C. Test is safer than alternative strategies
- D. Test reduces patient's or clinician's uncertainty
- E. Test is expected to be abnormal in presence of patient's already confirmed diagnosis

Answer: E Tests should be ordered when they are expected to change care and should be chosen on basis of safety, cost, and impact. They should not be ordered simply because they can confirm an already known diagnosis.

Ch / 12 QUALITY OF CARE AND PATIENT SAFETY

1. Which one of the following is the current number of randomized clinical trials published each year?

- A. 1000
- B. 5000
- C. 13,000
- D. 19,500
- E. 27,000

Answer: E Without discounting the value of experience and mature clinical judgment, the modern paradigm for determining optimal practice has changed, driven by the explosion in clinical research during the past 30 years; for example, the number of randomized clinical trials grew from 350 per year in 1970 to more than 27,000 per year in 2012.

2. Which one of the following would *not* be characterized as process measures under Donabedian triad?

- A. Fraction of patients with myocardial infarction who received β -blockers
- B. Fraction of patients with stroke who died within 30 days (risk adjusted)
- C. Fraction of hospitalized patients with pneumonia given pneumococcal vaccination
- D. Fraction of hospitalized patients with heart failure with documented predischARGE instructions
- E. Fraction of diabetic outpatients who received eye examinations

Answer: B Many of the widely used quality measures are process measures for which clinical research has established a link between such processes and improved outcomes. An example is the rate at which aspirin or a β -blocker is given to survivors of a myocardial infarction before hospital discharge (Chapter 73). However, when processes are less relevant and the science of case-mix adjustment is suitably advanced (e.g., cardiac bypass surgery; Chapter 74), outcome measurement (e.g., risk-adjusted mortality rate or 30-day readmission rate) is increasingly used. In other areas involving complex processes, structural measures are used as proxies for quality; examples here include the presence of intensivists to staff critical care units, a dedicated stroke service, and computerized physician order entry (CPOE) systems.

3. Which of one the following is a policy lever that has been used to promote improved quality and safety?

- A. Public reporting of performance
- B. Pay for performance
- C. No pay for errors
- D. Appeal to professionalism
- E. All of the above

Answer: E The recent recognition of major gaps in quality and of the need for systemic change to improve quality has led to a variety of initiatives to catalyze quality improvement. Virtually all involve several steps: defining reasonable quality measures (evidence-based measures; capturing appropriate structures, process, or outcomes), measuring the performance of providers or systems, and using these results to promote change. This final imperative creates the greatest degree of uncertainty and experimentation.

Although one might hope that simply giving a physician information about prior performance would generate meaningful improvement, this strategy yields only modest change at best. Increasingly, a more aggressive and transparent strategy, such as disseminating the results of quality measurement to key stakeholders, is being adopted. In some cases, simple transparency is the main strategy—the rationale being that providers will find the exposure of their gaps in quality to be sufficiently concerning or embarrassing to motivate improvement. Although there is little evidence that patients use such data to choose among physicians or hospitals, transparency itself has frequently resulted in impressive improvements in some publicly reported quality measures.

The newest strategy in the United States is to tie payments for service to quality performance (pay for performance, or P4P). A number of P4P programs are under way, and early results indicate that differential payment leads to surprisingly modest gains beyond the improvements achieved by simple transparency (Jha AK, Joynt KE, Orav EJ, Epstein AM. The long-term effect of Premier pay for performance on patient outcomes. *N Engl J Med*. 2012;366:1606-1615). P4P also raises a host of concerns, including whether presently captured quality data are accurate, whether payments should go to the best performers or those with the greatest improvements, whether existing measures adequately measure quality in patients with complex diseases, and whether P4P will create undue focus on certain measurable practices, leading to relative inattention to other important processes that are not being compensated. The behavioral economics literature also warns that an over-emphasis on “extrinsic” motivation (i.e., bonus payments) can actually extinguish “intrinsic” motivation (i.e., professionalism). One variation on the P4P theme is Medicare’s “no pay for adverse events” program, in which hospital payments are withheld for certain “preventable” adverse events such as injuries from falls or health care–associated infections (Jack BW, Chetty VK, Anthony D, et al. A reengineered hospital discharge program to decrease rehospitalizations: a randomized trial. *Ann Intern Med*. 2009;150:178-187). As with P4P more generally, the impact of such programs on quality and safety has been surprisingly modest.

4. The “Swiss cheese model” for patient safety refers to which one of the following?

- A. The importance of ensuring that the workforce is well fed and rested
- B. The ability of Swiss trains and watches to run on time
- C. The observation that many errors relate to the failure of multiple incomplete layers of protection
- D. The inadequate incentives to promote safety
- E. The tendency for computer systems to create new classes of errors

Answer: C The “Swiss cheese” model of accidents, drawn from innumerable investigations of accidents in commercial aviation and the nuclear power industry, for example, emphasizes that single errors by one individual working in an otherwise safety-conscious system rarely cause harm. Instead, such errors must penetrate multiple incomplete layers of protection (“layers of Swiss cheese”) to cause terrible harm. The lesson is to focus not on the futile goal of trying to perfect human behavior but rather on creating multiple overlapping layers of protection to decrease the probability that the holes in the Swiss cheese will ever align, allowing an error to slip through.

5. Which one of the following would be an accurate equation to capture health care “value”?

- A. $\text{Quality} \times \text{safety} \div \text{patient satisfaction} \times \text{cost}$
- B. $\text{Quality} \div \text{patient satisfaction} \times \text{cost} \times \text{safety}$
- C. $\text{Cost} \div \text{quality}$
- D. $\text{Quality} \times \text{safety} \times \text{patient satisfaction} \div \text{cost}$
- E. $\text{Quality} \times \text{cost} \div \text{patient satisfaction}$

Answer: D Outside of health care, most purchasing decisions are based on perceived value: $(\text{quality} + \text{safety}) \div \text{cost}$. Health care decisions historically have not been made this way, in part because of the limited ability of patients and payers to make rational judgments about the quality and safety of a given provider or system, and in part because health care insurance insulates patients from the full cost of care. In the United States, which spends nearly 20% of its Gross Domestic Product on health care, policy pressures are increasingly being brought to bear on the entire value equation (“promoting value, not volume”). For example, Medicare’s Value-based Purchasing program modifies hospital reimbursement based on quality, safety, and patient satisfaction scores.

Ch / 13 COMPREHENSIVE CHRONIC DISEASE MANAGEMENT

1. An obese patient with type 2 diabetes consistently has HbA1c levels above 10%. There is strong evidence that he is not following diet or exercise recommendations. He has recently attended diabetes education classes at the local hospital. Which of the following is the most appropriate next step?

- A. Collaboratively establish realistic goals and an action plan and monitor closely.
- B. Remind him of the dangers of uncontrolled diabetes.
- C. Increase his medications.
- D. Refer him to a diabetologist.

Answer: A It is highly likely that this gentleman's poor diabetes control is heavily influenced by his poor self-management. Before changing or increasing drug therapy, it would be most appropriate to have him spend time with someone (preferably in the practice) trained to use effective counseling methods like motivational interviewing to try to motivate him, develop achievable behavioral goals and a realistic action plan, and then follow him closely.

2. A physician receives performance metrics about her care of diabetes and hypertension. She is disappointed to find that her measures are below the average for her practice, even for simple things that she thought she was diligent about—for example, flu shots and regular HbA1c testing. She can't work any harder. Which of the following is the most appropriate next step?

- A. Increase the time allotted for visits by diabetic or hypertensive patients.
- B. Try to increase the involvement of her medical assistant and other available staff in the performance of evidence-based care.
- C. Hire a nurse to manage routine diabetes and hypertension visits.
- D. Add more frequent alerts to her EMR.

Answer: B There is considerable evidence that the involvement of all members of the practice team in meeting patient needs is the intervention that leads to the largest improvements in the delivery of evidence-based services and disease control for hypertensive and diabetic patients. Medical assistants and LPNs can review patient records before visits to identify needed services and, with standing orders, perform all those functions that state regulations allow. They can also be trained to provide self-management support.

3. Local health plans are providing performance bonuses to practices that can demonstrate reductions in their readmission rates for chronically ill patients. Which of the following is most likely to help a practice reduce their readmission rate?

- A. Have practice clinicians make hospital rounds.
- B. Tell patients to call for an appointment after discharge.
- C. Hire and/or train a nurse care manager in the practice to work with recently hospitalized patients.
- D. Ask hospital discharge planners to alert the practice that their patient is ready for discharge.

Answer: C Hospital readmissions can be reduced by ensuring timely, coordinated, and appropriately intensive post-hospital care. Hospitals often don't or can't identify a patient's primary care provider, so community practices must proactively try to identify hospitalized patients and make certain that they receive appropriate follow-up care. A care manager working in or closely with primary care is the best option.

4. Major depression is a common problem seen primarily in primary care. A practice is trying to develop local guidelines for the management of patients with this condition. They are trying to take into account the evidence of effectiveness as well as patient preferences and costs. Which of the following is the best strategy for them to employ?

- A. Refer all patients either to a psychiatrist or therapist depending on patient preference.
- B. Refer patients that don't respond to initial therapy to a mental health provider.
- C. Give all patients a trial of antidepressant medication.
- D. Identify a mental health provider consultant and care manager within to practice to help the primary care physicians manage the patients.

Answer: D There is very strong evidence that collaborative care models are superior to other ways of managing depressed patients in primary care. These models include ensuring that primary care physicians understand treatment guidelines, that staff in the practice are trained to provide follow-up assessments for depressed patients, and that a mental health provider is available to provide information and support to the primary care physician or care manager, and to see patients if necessary.

Ch / 14 COUNSELING FOR BEHAVIOR CHANGE

1. Which of the following statements best describes the purpose of change counseling in the context of medical care?

- A. To evoke patient self-motivation and to resolve ambivalence about changing
- B. To advise patients of the evidence-based changes that are best for their health
- C. To affirm and to support the autonomy of patients regardless of whether they change
- D. To make patient-centered arguments to convince patients to change
- E. To create a safe supportive environment that encourages patient change

Answer: A The principles of change counseling emphasize the importance of goal-directed counseling that ends in the patient's moving toward more healthy behaviors. The approach uses conversational counseling methods that evoke the patient's motivation and resolve natural ambivalence between the status quo and the effort needed to change. Therefore, A is the best answer. B is wrong because counseling is more than giving advice. C speaks to supporting the patient's autonomy, which is important, but not to making progress toward change. D is wrong because argument is specifically avoided in change counseling and is a sign of dysfunction in the patient-physician relationship. E is important for counseling, but it does not go far enough in defining the goals of change counseling.

2. Which of the following motivational interviewing skills are most useful in helping patients explore their ambivalence and talk themselves into changing?

- A. Giving clear, simple explanations about medical conditions and the changes people can make to reduce the risks to their health
- B. Using open questions and statements of affirmation and reflection to guess a patient's meaning and summarizing a patient's perspectives
- C. Obtaining a complete assessment of risks, prior patient behaviors, and experiences with making other changes in their lives
- D. Using the conviction-confidence ruler to assess the patient's reasons for changing and reasons for sustaining the status quo
- E. Acknowledging nonverbal emotion caused by clinicians giving advice or telling patients what to do

Answer: B B is the correct answer because it states the four skills that characterize motivational and most patient-centered interviewing: open questions, affirmation, reflection, and summarization. Although a health risk assessment is an important starting point for change counseling, A is incorrect because it is limited to giving advice. C is incorrect because obtaining an assessment, although important, is only part of the task. D is incorrect because the purpose of the conviction-confidence ruler is to assess motivation, and D describes decisional ambivalence. Acknowledging emotions is an important engagement skill, but E is incorrect because the answer is limited to advice given by clinicians.

3. What is the purpose of a decisional balance tool in change counseling?

- A. It shows the balance of risks of disease and benefits of treatment.
- B. It documents the clinician's decisions for the changes patients need to make.
- C. It tracks change in the patient's confidence during the course of counseling.
- D. It demonstrates the patient's perceived importance of making a change.
- E. It displays a patient's ambivalence between making change and sustaining the status quo.

Answer: E E is correct. The decisional balance is a counseling tool that displays a patient's ambivalence, showing the arguments for sustaining the status quo in one column and the arguments for change in an adjacent column. It is a potential starting point for change counseling in the precontemplation and contemplation stages. A is incorrect because the decisional balance is not about the clinician's decisions. B is not correct; although putting the decisional balance in the medical record documents its use and its results, decisional balance displays the patient's ambivalence, not the physician's decisions. C is wrong because the decisional balance displays ambivalence and does not track changes in commitment. D is partially correct because the decisional balance documents the patient's reasons for change, but it also documents the reasons for sustaining the status quo.

Ch / 15 THE PERIODIC HEALTH EXAMINATION

1. A 40-year-old married woman comes for her periodic health examination. She has had negative annual Pap tests for the last 5 years. Which of the following options describes a recommended strategy for cervical cancer screening?

- A. Obtain a human papillomavirus (HPV) test along with the Pap test; if both are normal, no screening will be needed for 5 years.
- B. Because her last Pap was normal, defer Pap testing until next annual examination.
- C. Continue annual screening until the age of 64 years.
- D. Continue annual screening until age 50 years.
- E. Begin annual HPV testing but lengthen the interval for Pap testing to every 5 years.

Answer: A In the absence of HPV testing, every-3-year Pap testing is recommended by the U.S. Preventive Services Task Force (USPSTF) and the American College of Obstetrics and Gynecology (ACOG) for women with previously normal Pap tests. In women who are HPV negative, the interval can safely be extended to every 5 years. Co-testing (combined Pap and HPV testing) at 5-year intervals is recommended by the USPSTF and ACOG beginning at the age of 30 years and extending to age 65 years.

2. A 52-year-old woman is new to your practice. She is a lifelong nonsmoker, and she had her first mammogram in the past year, with normal results. She has never undergone colorectal cancer screening. Which of the following is true regarding recommendations for screening and options available to her?

- A. As an average-risk adult, she could be offered screening with any of the following options, which differ in their risks, intervals, and burdens of testing: high-sensitivity fecal occult blood testing (FOBT), flexible sigmoidoscopy with FOBT, or colonoscopy.
- B. Regular colorectal cancer screening in adults should stop at age 65 years.
- C. Computed tomography (CT) colonography at 10-year intervals is an acceptable option in place of colonoscopy.
- D. Colonoscopy every 5 years is the preferred option because of its higher sensitivity.
- E. Flexible sigmoidoscopy at 5-year intervals should be combined with annual FOBT.

Answer: A The U.S. Preventive Services Task Force (USPSTF) recommendations are based on a review of original studies and a commissioned comparative model to determine optimal age for starting and stopping screening for colorectal cancer and the optimal intervals. USPSTF recommendations suggest beginning screening at age 50 years and stopping regular screening at age 75 years. Their analyses indicated that either (1) annual high-sensitivity fecal occult blood testing (FOBT), (2) flexible sigmoidoscopy every 5 years combined with FOBT every 3 years, or (3) colonoscopy every 10 years would yield similar benefits over a population. CT colonography every 5 years and double-contrast barium enema every 5 years are included options in the 2008 guidelines of the Multisociety Task Force because of their ability to detect both cancer and polyps.

3. A 62-year-old African American man comes in for his first visit. Other than a 5-year history of high blood pressure, he is in good health. In response to questions about whether he should get a prostate-specific antigen (PSA) test, which of the following statements reflects information that should be part of a shared decision-making discussion?

- A. As an African American, he has a higher risk for prostate cancer but may not benefit more from screening compared with men of other ethnic backgrounds.
- B. PSA screening has been shown to reduce mortality from prostate cancer in some studies.
- C. False-positive PSA tests are common and may require a biopsy.
- D. PSA testing may result in detection and treatment of a cancer that would not have caused clinical problems (overdiagnosis).
- E. All of the above

Answer: E Although African American men do have an increased risk for prostate cancer, there is no evidence that benefits of screening are any higher in this group. PSA testing was associated with lower prostate cancer mortality in one European study, in which 48 men needed to be treated for every 1 death prevented after 9 years. By comparison, mortality was not significantly lower in a large American trial. False-positive PSA results and potential overdiagnosis are the major concerns regarding prostate cancer screening. As a result, none of the major organizations recommends routine screening with PSA, although some recommend a shared decision-making approach (<http://www.auanet.org/education/guidelines/prostate-cancer-detection.cfm>).

4. A 58-year-old male accountant comes in for a periodic examination. He is recently divorced and has a steady female partner with whom he is sexually active. Because his partner is postmenopausal, they do not use condoms. He has never been screened for any sexually transmitted diseases and has no symptoms nor history of any drug use or transfusions. Which of the following tests are indicated as a screening test?

- A. HIV
- B. Hepatitis C
- C. Chlamydia
- D. Gonorrhea
- E. Hepatitis B

Answer: A and B HIV testing is indicated in all adults who have never been screened. Although the subject has no specific risk factors for hepatitis C, testing is recommended for adults in his age cohort (born between 1945 and 1965). Chlamydia and gonorrhea screening might be indicated for a woman based on having a new sexual partner but is not recommended for men. Hepatitis B screening is recommended only for high-risk groups in nonpregnant adults.

5. A 40-year-old nonsmoking man is seen for his periodic examination. He has a healthy weight (body mass index = 20), blood pressure of 118/78 mm Hg, and no history of diabetes, and he is able to exercise regularly without symptoms. Last year, his nonfasting total cholesterol was 232 with an HDL of 50. Which of the following represents appropriate steps to address cardiovascular prevention in this patient?

- A. Perform a baseline electrocardiogram to look for evidence of ischemia or ventricular hypertrophy.
- B. Obtain a fasting lipoprotein analysis.
- C. Recommend he begin a daily low-dose aspirin regimen.
- D. Calculate his 10-year risk for cardiovascular disease to assess need to consider further interventions.
- E. Obtain a coronary computed tomography (CT) to look for evidence of calcifications

Answer: D Ten-year cardiovascular risk can be calculated using age, gender, lipids, blood pressure, and history of diabetes and smoking. This patient's 10-year risk is only 1.3%, putting him in a low-risk category; any benefits of aspirin will be offset by risks for gastrointestinal bleeding. Fasting lipoprotein analysis, although it will allow you to assess triglyceride and LDL cholesterol, is not needed because risk calculators require only total cholesterol and HDL. Neither ECG nor coronary CT is recommended by the U.S. Preventive Services Task Force as screening tests for coronary disease. Because findings on coronary CT are associated with risk for coronary events, some organizations suggest this test can be considered in patients who are near a threshold for considering statin therapy (7.5% 10-year risk for cardiovascular disease).

Ch / 16 PHYSICAL ACTIVITY

1. A 50-year-old man seeks advice about increasing his level of physical activity. While reading about exercise on the Internet, he noted that several websites advised: “consult your physician prior to starting an exercise program.” Currently, he rarely engages in moderate to vigorous physical activity, except occasionally on weekends when he does several hours of yard work. He has experienced gradual weight gain over the past two decades, and his body mass index is 28. His medical history is unremarkable except for high blood pressure, which is well controlled by hydrochlorothiazide. He is specifically interested in advice about exercise-related injuries. As a young man, he jogged regularly but had problems with pain in his knees. He also hopes he can lose weight by exercising more. Based on the history and the *2008 Physical Activity Guidelines for Americans*, which of the following statements is appropriate to include in your advice to this man?

- A. He should regularly perform moderate to vigorous intensity aerobic activity. He should choose a type or types he prefers and spread the aerobic activity throughout the week.
- B. To determine the intensity (level of effort) of his activity, his only option is to monitor his heart rate.
- C. Vigorous-intensity activity is preferable in adults his age. His goal should be to get at least 60 minutes of vigorous activity each week.
- D. Aerobic activity is important, but he should also do muscle strengthening exercises (such as weight training) 3 days per week, with two sets of 10 repetitions for each muscle group.
- E. If he is considering getting his physical activity by walking, his goal should be to walk at least 30 minutes a day on at least 5 days per week.

Answer: A This advice is relevant given the man’s history of concentrated yard work because the guidelines explicitly discourage large amounts of physical activity in a single day (so-called weekend warriors). B is incorrect because adults can use either absolute or relative intensity to guide their level of effort (heart rate monitoring is the most common way to assess relative intensity). C is incorrect in two ways—the guidelines do *not* state that vigorous activity is preferable, and the guidelines for vigorous activity are 75 minutes per week. D is incorrect in two ways—muscle strengthening exercises need to be on only 2 days per week, and the key guidelines do not have a requirement for two sets for each muscle group. E is incorrect because the current guidelines no longer require physical activity on “most days of the week” or “at least 5 days per week.”

2. In asymptomatic healthy adults, an evidence-based approach to reducing the risk for activity-related injuries includes which of the following?

- A. Gradually increasing the physical activity level over time
- B. Prescribing flexibility exercises
- C. Screening for coronary artery disease using either an exercise test or electron-beam computed tomography
- D. Starting with supervised exercise and then transitioning to unsupervised
- E. None of the above

Answer: A Gradually increasing physical activity over time is a key guideline for injury prevention. There is no evidence that flexibility exercises have health benefits, including no evidence that they prevent injuries. The U.S. Preventive Services Task Force does not recommend routine screening for coronary artery disease using an exercise treadmill test or using electron-beam computed tomography. There is insufficient evidence that supervised exercise reduces injury risk in healthy adults.

3. Which one of the following statements about the benefits and risks of physical activity is true?

- A. The overall risk for sudden death is higher in people who exercise regularly.
- B. The total volume of physical activity is the main determinant of health benefits.
- C. Obese adults do not obtain benefits from physical activity unless they lose weight.
- D. The benefits of being active at less than recommended levels are so small that it is of little value to recommend and promote physical activity in people who are not capable of meeting guidelines.

E. The benefits of increasing physical activity do not depend on current level of activity. A person who increases physical activity from 0 minutes to 30 minutes a day obtains the same health benefits as a person who increases activity from 120 minutes a day to 150 minutes per day.

Answer: B The overall risk for sudden death is lower in people who have a higher total volume of exercise. The health benefits of physical activity are independent of other risk factors, and obese adults obtain benefits from physical activity even if obesity persists. Consistent with the dose-response effect, there are meaningful benefits from obtaining less than the recommended amounts of activity. There is a curvilinear dose-response relationship, and the marginal health benefits of increasing activity are less at high levels of physical activity.

4. Which one of the following is recommended for the promotion of physical activity in clinical settings?

- A. Counseling and assisting virtually all patients to be physically active with techniques such as motivational interviewing
- B. Recommending people start with moderate-intensity activities such as walking, but advising virtually all patients gradually to shift to doing mainly vigorous intensity activity
- C. Paying little attention to community resources such as access to parks, gyms, and multiuse trails because there is little scientific evidence that they influence activity
- D. Advising virtually all patients to engage in regular physical activity, with the specific activity recommendation based on integrating public health guidelines for prevention with any applicable therapeutic guidelines
- E. Emphasizing exercise prescription and exercise classes because most people prefer these activities over lifestyle activities such as walking for transportation and gardening

Answer: D The physician should advise patients regarding the types and amounts of activity appropriate for them, specifically taking into account chronic diseases and activity limitations in making these recommendations. The U.S. Preventive Services Task Force does not recommend exercise counseling for all patients. There is strong evidence that access to community resources affects physical activity levels. Most patients prefer home-based exercise rather than exercise classes. Vigorous activity is not recommended for all adults.

5. Which one of the following statements is true about the use of physical activity to reduce the risk for falls and functional limitations?

- A. In overweight and obese older adults with physical functional limitations, weight loss is more important than physical activity in improving function.
- B. The fact that falls are more likely during activities such as walking explains why exercise programs in older adults do not reduce risk for falls.
- C. Because gait speed in older adults is mainly determined by leg length, it is not a useful measure of mobility or mortality risk.
- D. Low fitness (low exercise capacity) does not significantly affect the risk for mortality and is mainly important because it causes functional limitations.
- E. Performing Tai Chi exercises can reduce the risk for falls in elderly people.

Answer: E Tai Chi is an evidence-based method for reducing the risk for falls in elderly people. Weight loss is not more important than physical activity in promoting function. Exercise programs, including balance exercises, reduce the risk for falls. Exercise increases gait speed, and better gait speed is a strong predictor of lower mortality. Low physical fitness is associated with higher mortality.

Ch / 17 ADOLESCENT MEDICINE

1. A mother brings her 11-year-old daughter to see her physician because she is worried that her daughter has not started puberty. The physician performs a complete physical examination and assures the mother and her daughter that she has started puberty. What is the first visible sign of puberty among girls?

- A. Linear growth spurt
- B. Menarche
- C. Thelarche, the development of breast buds
- D. Pubarche, first appearance of pubic hair
- E. Weight gain

Answer: C The first visible sign of puberty among girls is usually thelarche, or the development of breast buds, which occurs on average at 10.5 years in white girls and 1 year earlier in African American girls.

2. A 14-year-old girl comes to see you because she has not started her menstrual period. The following statements about menarche are all true except which one?

- A. Menarche occurs 2 to 4 years after the initial appearance of breast buds and pubic hair.
- B. The average age of menarche is 12.9 years for white girls.
- C. The average age of menarche is 12.2 years for African American girls.
- D. Menstrual periods are always regular after the onset of menarche.
- E. At menarche, only 20% of cycles are ovulatory.

Answer: D Menarche, or the onset of the first menstrual period, occurs 2 to 4 years after the initial appearance of breast buds and pubic hair. The average age of menarche is 12.9 years for white girls and 12.2 years for African American girls. Menstrual periods are not always regular during the first 2 years after menarche. At menarche, only 20% of cycles are ovulatory; it may take up to 4 years for 80% of cycles to be ovulatory. The average length for the completion of puberty in girls is 4 years (range, 1.5 to 8.0 years).

3. An 18-year-old sexually active woman comes to see her physician for a Papanicolaou smear. Her current partner is her first and only sexual partner, and she reports that she and her partner are monogamous. She is taking the oral contraceptive pill and uses the condom every time she has sexual intercourse. In reviewing the most recent American guidelines for cervical cancer recommendations, you realize that performing a Papanicolaou smear does not apply to which of the following circumstances?

- A. Young women with symptoms of cervical cancer
- B. Women with previous abnormal test results on cervical screening
- C. Women who are immunosuppressed by HIV, organ transplantation, chemotherapy, or chronic use of corticosteroids
- D. Sexually active women who are practicing safe sex

Answer: D The most recent American guidelines for cervical cancer screening recommend against screening of women younger than 21 years. These recommendations do not apply to young women with symptoms of cervical cancer or previous abnormal test results on cervical screening or to women who are immunosuppressed by HIV, organ transplantation, chemotherapy, or chronic use of corticosteroids. (Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin.* 2012;62:147-172.)

4. You are working at a university health center caring for students. You learn that this semester a 20-year-old student died of testicular cancer (student A), a 23-year-old student committed suicide (student B), and a 19-year-old student was killed in a car accident (student C). Which of these three students fall in the top three causes of death in young adults?

- A. Students A and B (cancer and suicide)
- B. Students B and C (suicide and car accident)
- C. Students A and C (cancer and car accident)
- D. All three students (cancer, suicide, and car accident)
- E. None of the students

Answer: B The top three causes of death in adolescents and young adults are unintentional car accidents (most from motor vehicle accidents), suicides, and homicides. These three cause more than 71% of deaths in adolescents and young adults. Cancer deaths in this age group are a distant fourth cause of mortality (see Table 17-1). (Hoyert DL, Xu J. Deaths: preliminary data for 2011. *National Vital Statistics Reports*. Hyattsville, MD: National Center for Health Statistics; 2012.)

Ch / 18 IMMUNIZATION

1. Tdap vaccine is recommended to be given only once for all groups except which of these?

- A. Pregnant women
- B. Parents of children younger than 2 years
- C. Adults 65 years of age and older
- D. Children 11 years of age or older who did not complete their DTaP vaccine series
- E. Adolescents and adults entering college

Answer: A Pregnant women should receive Tdap vaccine during each pregnancy to offer protection to each newborn. Available data indicate fairly rapid waning of pertussis immunity after Tdap vaccination and no significant adverse events after repeated Td or Tdap vaccinations with short intervals between them. For more information, see <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6207a4.htm>.

2. Persons who are at increased risk of meningococcal disease and for whom meningococcal vaccine is recommended include all except which of the following?

- A. Persons without spleens or whose spleens are not functional (e.g., have sickle cell disease)
- B. Persons with persistent complement deficiencies
- C. Persons 65 years and older
- D. Microbiologists regularly working with *Neisseria meningitidis* isolates
- E. Persons traveling to sub-Saharan Africa

Answer: C Available data indicate increased risk of meningococcal disease for all the listed groups except persons 65 years and older. <http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf>.

3. Pneumococcal conjugate vaccine is recommended for which of these adult groups?

- A. Persons with nephrotic syndrome
- B. Persons with liver cirrhosis
- C. Persons with chronic obstructive pulmonary disease
- D. Persons with coronary artery disease
- E. Persons with diabetes

Answer: A Most of the additional benefit of pneumococcal conjugate vaccination, when it is used to supplement pneumococcal polysaccharide vaccination, accrues to persons with iatrogenic or disease-related immunocompromising conditions, including nephrotic syndrome, as well as persons with functional or anatomic asplenia, cerebrospinal fluid leaks, and cochlear implants. For more information, see <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6140a4.htm>.

4. Adults at increased risk of hepatitis B infection who should receive hepatitis B vaccine include which of the following?

- A. Persons with chronic obstructive pulmonary disease
- B. Persons with coronary artery disease
- C. Persons with nephrotic syndrome not on dialysis
- D. Persons 19 to 59 years old with diabetes mellitus
- E. Persons 65 years and older

Answer: D Persons who have frequent contact with contaminated blood or body fluids are at increased risk of hepatitis B infection. Adults 19 to 59 years of age with diabetes mellitus also are at increased risk of hepatitis B infection, at least in part because of poor infection control practices with assisted blood glucose monitoring (see <http://www.cdc.gov/mmwr/pdf/wk/mm6050.pdf>). Therefore, the Centers for Disease Control and Prevention recommend that adults with diabetes mellitus younger than 60 years receive hepatitis B vaccine.

5. Human papillomavirus (HPV) vaccine is recommended for

- A. Routine and catch-up vaccination for boys beginning at 11 years and men through 21 years
- B. Persons 65 years and older
- C. Only men who have sex with men
- D. Girls and women 11 to 50 years
- E. Girls and boys beginning at 9 years of age

Answer: A HPV vaccine is recommended for persons primarily before they begin sexual activity and have been infected with HPV. The upper age range for both licensed vaccines is 26 years. Although the vaccine is licensed for both boys and girls beginning at the age of 9 years, it is recommended to begin at age 11 to 12 years, at the same time as other adolescent vaccines (Tdap and meningococcal vaccines). For more information, see <http://www.cdc.gov/mmwr/pdf/wk/mm6050.pdf> and <http://www.cdc.gov/mmwr/PDF/wk/mm5920.pdf>.

1. A 35-year-old carpenter complains of new-onset headaches shortly after beginning a new job in a small boat-refurbishing shop. His job involves cleaning debris from the hulls of sailboats and resurfacing them. What is the most useful approach to establish whether some exposure or condition in the shop is causing his headaches?
 - A. Proceed as with any new headache evaluation. Then, once a diagnosis is made, explore online toxicologic databases to see if any chemicals are known to cause such a headache pattern.
 - B. Ask the patient to obtain a complete list of all chemicals and processes in the shop and research each to see if it can cause headaches.
 - C. Question the patient closely about the temporal relationship between work activities and symptoms.
 - D. Test the patient's blood and urine for common industrial solvents likely to be used in his work.
 - E. Call the employer to inquire if other workers have made similar complaints in the past.

Answer: C For the assessment of acute symptoms in relation to an environmental exposure, the history of temporal relationship between exposure and onset/cessation of symptoms is the most compelling basis for pursuit of a work connection for a new complaint. If headaches typically occur after arriving at work or starting a specific activity and are absent at other times, the physician should obtain a detailed list of chemicals or other potential culprits and explore their toxicology.

2. Which of the following is true regarding the relevance of "dose of exposure" to a workplace or environmental chemical?
 - A. Unlike pharmaceuticals, environmental toxins typically cause injury in susceptible people irrespective of the actual dose.
 - B. Unlike with pharmaceuticals, the possible doses to which a worker might be exposed at work range over many orders of magnitude.
 - C. Unlike with pharmaceuticals, there is no simple way of estimating exposure dose from talking to a patient; the workplace or exposure environment itself must be evaluated.
 - D. Unlike pharmaceuticals, environmental toxins typically affect everyone exposed in a similar way.
 - E. Unlike with pharmaceuticals, blood and urine levels are the mainstay for assessing exposure dose to chemicals.

Answer: B For drugs and toxins, dose matters. What differs is the sheer number, probably 100,000 or more, of different chemicals and the enormous range of possible exposure doses, from trivial parts per billion or trillion in a well-controlled environment to gram quantities in an unventilated workplace or in an accidental release. However, as noted in the text, strong inference about the range of exposure dose can be made from talking to the patient; directly measuring the environment and biomarkers of exposure is rarely the first-line approach. As with drugs, idiosyncratic responses are common, and no two people respond alike.

3. Which of the following is true regarding occupation-related asthma?
 - A. Nonatopic individuals with previously normal respiratory health may develop de novo sensitivity to one of hundreds of workplace proteins, metals, or other chemicals.
 - B. Smokers and atopic individuals are the ones most likely to develop airway reactions at work. Cough or wheeze in the presence of one or more such risk factors demands *increased* vigilance about workplace exposures.
 - C. Workplace factors cause or exacerbate asthma in up to 20% of adult-onset asthma cases.
 - D. A and C
 - E. A, B, and C

Answer: E Work exposures commonly cause airway lability in susceptible individuals, sometimes by primary sensitization in atopic or nonatopic men and women and sometimes by irritating already abnormal airways in smokers

and patients with preexisting airway disease. Most studies estimate that almost one in five newly symptomatic adult asthmatics has an occupational or environmental cause, so this possibility must

always be explored because an overlooked and preventable exposure may lead to lifelong, irreversible injury.

4. A 60-year-old woman is admitted to the hospital with new onset of a large pleural effusion and incapacitating chest pain. What is the best approach to determine if a work exposure may have been involved?

- A. Perform a detailed occupation and environmental history of *current* exposures on admission to identify a possible cause for malignant or nonmalignant disease consistent with the presentation, such as asbestos.
- B. Perform a detailed occupation and environmental history of *past* exposures on admission to identify a possible cause for malignant or nonmalignant disease consistent with the presentation, such as asbestos.
- C. Proceed with the evaluation as you would for any patient with the observed constellation of signs and symptoms. Take a detailed environmental history of current and past exposures *after* a pathologic diagnosis has been made, focusing on established causes of that diagnosis, for example, lung cancer.
- D. After the evaluation, ask the laboratory to analyze surgical and other specimens for evidence of fibers or metals that are known to cause the patient's diagnosed condition.
- E. After the diagnosis is made, seek information from the local health department or similar agencies about the occurrence of similar cases in the area because patients are unlikely to recall what they were exposed to years before.

Answer: C In the assessment of a new-onset chronic disease, it is not efficient to take an exhaustive history of either current or former exposures as the evaluation will quickly reveal a clear target (diagnosis) on which to focus. Although recognition of a prominent work exposure, such as asbestos, might make the possibility of malignant mesothelioma more likely in this case, it is still necessary to make a pathologic diagnosis before worrying about its cause. This approach is in contrast with the approach to new onset of acute or recurring symptoms (question 1). D and E are important in some cases, but the first and most direct approach is to inquire whether the patient may have been exposed to the (invariably) small number of substances known to cause the just-diagnosed condition. These lists can easily be found in reference texts or online search tools (e.g., "occupational causes of lung cancer").

5. Which of the following is true of musculoskeletal disorders among working-age patients?

- A. Because these disorders are most often associated with nonspecific findings on examination or imaging studies, they rarely lead to significant dysfunction or disability.
- B. Now that most work in developed economies is less physical, musculoskeletal disorders have become relatively rare.
- C. The best approach to prevent long-term disability is early recognition, intensive evaluation, and definitive treatment where possible.
- D. Assessment and modification of offending work activities are more important in the long run than is a definitive anatomic diagnosis.
- E. When a musculoskeletal disorder is recognized, the best way to establish whether it is related to work activity is to visit the workplace or to call the employer.

Answer: D Musculoskeletal disorders remain extremely common and extremely disabling even in highly developed economies and in jobs—like health care, food service, and education—that are not intensely physical. The key to diagnosis is the relationship between physical activities at work, which the patient can easily demonstrate to the physician, and the pattern of symptoms and signs. Intervening in the work by job modification or change is far more valuable in the long run than finding a drug or surgery to control the symptoms, which often recur when the patient returns to the old environment and tasks.

Ch / 21 BIOTERRORISM

1. An air detector in your city has indicated that there has been an aerosol attack with smallpox. This has been verified by the state health department. You are seeing a number of individuals suspected of having been exposed during the attack that occurred 3 days ago. What would be the appropriate management for these individuals?

- A. Give vaccinia immune globulin at the earliest opportunity.
- B. Vaccinate exposed individuals with the smallpox vaccine (ACAM2000).
- C. Vaccinate exposed individuals with the smallpox vaccine, except those with eczema.
- D. There is nothing you can offer at this point except reassurance.
- E. You can treat them with cidofovir.

Answer: B Studies of historical outbreaks have demonstrated that after individuals are exposed to smallpox, it has been possible to prevent or to ameliorate smallpox disease by vaccination. When it is administered by scarification, replication of the smallpox vaccine (vaccinia virus) can provide immunity faster than the replication of the variola (smallpox) virus. However, the vaccination must occur relatively quickly after exposure, usually within 4 or 5 days, to have maximum likelihood of benefit. Although the vaccine can cause adverse effects in immunocompromised people and individuals with skin disorders, such as eczema, there are no contraindications to vaccination in the event of a true exposure. Cidofovir is potentially nephrotoxic and has been used for treatment but not for prevention. Vaccinia immune globulin is primarily used for treatment of vaccine adverse events, not for smallpox disease. Finally, a newer vaccine, modified vaccinia Ankara, which is believed to have less risk for immunocompromised individuals, is under study as a potential alternative.

2. You become aware of a large outbreak of nontyphoidal *Salmonella* in your community. Which of the following is not true?

- A. More cases than would be expected in the community might be a clue of intentional spread.
- B. A genetic match between patient isolates, a laboratory at a suspicious local cult, and local salad bars may indicate intentional spread.
- C. This outbreak is unlikely to be spread intentionally because *Salmonella* is not considered a high-threat agent.
- D. Disease in a specific ethnic group may indicate intentional targeting of the infectious agent.
- E. An unusual antibiotic susceptibility pattern of the organism might indicate intentional tampering.

Answer: C Public health authorities have designated certain organisms as most concerning (category A agents) on the basis of characteristics such as the ability to grow in large quantities, stability in aerosol, and ability to infect by the aerosol route. However, we are unable to understand a specific perpetrator's criminal intentions; the perpetrators may not have access to such classic bioweapon agents, and they may instead use an organism that is easier to obtain. This is what occurred in the Dalles, Oregon, outbreak in 1984, when the Rajneesh cult contaminated local salad bars with *Salmonella typhimurium*. These types of outbreaks are difficult to pinpoint as artificially caused, so it is useful to look at historical outbreaks and potential clues as to why this might deviate from what would be expected.

Ch / 22 CHRONIC POISONING: TRACE METALS AND OTHERS

1. A 58-year-old patient seeks your care for management of his hypertension. In his evaluation, you discover that he operates a gun range and often cleans up casings at the end of the day. You request a blood lead level that comes back elevated at 60 µg/dL. He has no other medical complaints. Along with pharmacologic management for his hypertension, which of the following lead treatment strategies would be the most efficacious?

- A. Chelation with BAL and CaNa₂EDTA
- B. Chelation with DMSA
- C. Chelation challenge, and if the 24-hour urine level is above 100 µg per gram of creatinine, chelate with DMSA
- D. No intervention is warranted.
- E. Proper respiratory protection at work and repeat lead levels in 1 month

Answer: E Adults who are asymptomatic and have blood lead levels below 70 µg/dL require no treatment besides removal of the source of exposure and decrease in workplace exposure through proper respiratory protection.

2. A 38-year-old health-conscious man is referred to you for arsenic poisoning. He has been seeing his primary care physician for symptoms of mild depression. He asked his physician to check him for heavy metal poisoning because he has well water and read that lead could cause symptoms similar to his. A 24-hour urine test result showed lead and mercury levels to be within normal limits but revealed an extremely elevated urine arsenic level (530 µg per gram of creatinine). What is the most prudent next step?

- A. Admit him to the hospital and immediately begin chelation with DMSA.
- B. Ask about any history of seafood ingestion and send his urine for arsenic speciation.
- C. Begin outpatient treatment with DMSA and repeat testing in 3 weeks.
- D. Obtain blood arsenic levels to determine if he has had a recent exposure.
- E. Obtain hair arsenic levels to determine if he has had a remote exposure.

Answer: B Organic arsenic is considered largely nontoxic to humans. Found in shellfish and seafood, it is a common cause of elevated urinary arsenic levels. In patients without symptoms of acute arsenic poisoning, a detailed history of seafood ingestion and sending a urine sample for speciation of arsenic would be the next step.

3. A 32-year-old chemical worker ingests a vial of methylmercury in a suicide attempt. She is admitted to the hospital, lavaged, and begun on DMSA chelation. The development of which of the following symptoms would concern you the most in respect to her long-term outcome?

- A. Hypertension and tachycardia
- B. Myalgias
- C. Prolonged QTc on her electrocardiogram
- D. Proteinuria
- E. Visual field constriction and perioral numbness

Answer: E The most devastating effect of organic mercury intoxication is neural degeneration. Early symptoms of this include constriction of visual fields, tremor, and paresthesias. Symptoms can progress to ataxia and ultimately to encephalopathy and death. Elemental mercury exposure can mimic pheochromocytoma and can be manifested with muscle weakness and myalgias; these symptoms can improve when the source of mercury exposure is removed. Proteinuria would be a potential manifestation of inorganic mercury toxicity, but renal damage tends to resolve over time. Arsenic, not mercury, is associated with a prolonged QTc.

4. A 68-year-old Hispanic woman with end-stage renal disease requiring hemodialysis three times a week develops a progressive encephalopathy. The water used for dialysis was tested and found to be normal. Which one of the following would you think is most responsible for her symptoms?

- A. Occasional use of Pepto-Bismol
- B. A prosthetic hip joint
- C. Her sucralfate prescription
- D. The homeopathic use of colloidal silver
- E. Traditional Hispanic folk remedy for gastrointestinal distress

Answer: C Sucralfate is most likely to cause encephalopathy in a dialysis patient from aluminum toxicity. A prosthetic hip with cobalt has been linked to cardiomyopathy and hypothyroidism. Pepto-Bismol can cause a progressive encephalopathy but typically only after prolonged and regular use. Hispanic folk and Chinese herbal medicines can occasionally contain arsenic and elemental mercury, but either would be less likely to cause the patient's symptoms. Colloidal silver ingestion typically affects only the skin.

Ch / 24 GERIATRIC ASSESSMENT

1. A Physician Orders for Life-Sustaining Treatment (POLST) form orders must be respected in which of the following settings?

- A. Hospital
- B. Emergency department
- C. Skilled nursing facility
- D. Home (by emergency medical technicians)
- E. All of the above settings

Answer: E Physician Orders for Life-Sustaining Treatment forms must be respected in all settings of care.

2. For frail older persons, the most important determining factor of whether a specific preventive service (e.g., mammography, colonoscopy, bone mineral density assessment, cholesterol lowering for primary prevention of heart disease) should be provided is which of the following?

- A. Life expectancy
- B. U.S. Preventive Services Task Force recommendations
- C. Professional society (e.g., American College of Physicians) guidelines
- D. Pay-for-performance incentives

Answer: A If a patient is unlikely to live long enough to accrue the benefits of treatment, the preventive service is not indicated. Some guidelines issued by professional societies do not consider comorbidity or life expectancy. Pay-for-performance initiatives do not consider age. The U.S. Preventive Services considers life expectancy only based on current age and only for some recommendations.

3. Which of the following statements about functional status is incorrect?

- A. It is always impaired in dementia.
- B. Impairment of instrumental activities (e.g., shopping, managing finances, performing housework) is more common than impairment of basic activities (e.g., bathing, dressing, transferring).
- C. It can be assessed by self-report or direct observation.
- D. It has prognostic value in outpatient but not inpatient settings.

Answer: D Functional status has prognostic value in both outpatient and hospital settings. Functional impairment is required for the diagnosis of dementia and is used to differentiate dementia from mild cognitive impairment. Functional status can be assessed by self-report or objectively (e.g., by a physical or occupational therapist or with structured, performance-based instruments).

Ch / 25 COMMON CLINICAL SEQUELAE OF AGING

1. A 74-year-old man who is in robust health and who exercises frequently asks what supplements will keep him strong and fit. Which of the options has been proved effective in maintaining quality of life and fitness in older adults?

- A. Growth hormone
- B. Testosterone
- C. Vitamin D and calcium
- D. Regular exercise
- E. Coenzyme Q

Answer: D Many studies have evaluated the safety and efficacy of hormones and other treatments for maintenance of strength and function in older age groups. Although growth hormone, testosterone, and vitamin D may be helpful in those with diagnosed deficiencies, there is no evidence that giving these agents to a relatively healthy person without signs or symptoms of such deficits would be beneficial. Regular exercise is the only listed intervention that has been shown to be safe and efficacious for building strength and enhancing quality of life in almost any setting.

2. An 82-year-old patient presents with a chief complaint of “I just don’t have any energy.” He notes muscle wasting, fatigue, and functional decline during the past year. Extensive medical evaluation in the next month reveals no obvious medical conditions that explain this decline. What should you recommend?

- A. Careful medical monitoring
- B. Assessment of his risk for falling
- C. Exercise and activity regimen
- D. Social engagement
- E. All of the above

Answer: E This obviously frail patient is at high risk for adverse outcomes, social isolation, and mortality in the coming years. He warrants careful medical monitoring, assessment of the risk for falling, and increasing social engagement. In addition, exercise has been demonstrated to be helpful in even the frailest older adults. Hence, all of the answers are appropriate in this patient.

1. Which of the following is true about acute urinary retention in an older man?

- A. Indicates the need for surgical decompression
- B. Is treated effectively with α -adrenergic blockers
- C. Is treated effectively with bethanechol
- D. Requires treatment of the underlying urinary tract abnormality
- E. None of the above

Answer: E The differential diagnosis for urinary retention extends beyond urethral obstruction, particularly in elderly people. Many older patients may develop retention owing to a weak detrusor associated with age, autonomic neuropathy, or previous urethral obstruction. In addition, fecal impaction, pain (e.g., following hip replacement), and medications with urinary tract side effects (e.g., anticholinergics, sedating antihistamines, decongestants, opiates) may induce acute urinary retention, particularly in patients with underlying bladder weakness or obstruction. Thus, the bladder should be decompressed for at least a week while reversible causes are addressed; the larger the postvoid residual volume, the longer the decompression should be. Decompression allows some restoration of detrusor strength, which also facilitates urodynamic testing should it be necessary. α -Adrenergic blockers are effective for men with symptoms of prostatism, but clinical trials of its efficacy have excluded patients with significant urinary retention. Bethanechol has not proved effective in controlled clinical trials. Decompression in some elderly patients can reduce but not eliminate residual urine. Provided it does not cause symptoms or renal compromise, subclinical retention need not necessarily be treated in all elderly patients, even if obstruction is present.

2. A 58-year-old obese woman with significant daily stress incontinence comes for a follow-up appointment. Her bladder diary shows maximal voided volume of 125 mL during the daytime. Each of these measures is appropriate except which of the following?

- A. Adjustment of fluid excretion and voiding intervals
- B. Advise weight reduction
- C. Teach her postural maneuvers
- D. Consideration of surgical correction
- E. Pelvic floor muscle exercises

Answer: A Recent evidence suggests that weight loss will improve stress incontinence in obese women, and data support the use of postural maneuvers, pelvic floor muscle exercises, and surgical correction as well. Adjusting fluid excretion and voiding intervals can also be useful, especially for women with volume-dependent stress leakage. It can work particularly well for women with a threshold of at least 150 mL and best in those with a threshold of more than 250 mL. When the threshold for stress incontinence is this low, however, the extent of fluid restriction required is usually not feasible and might even lead to dangerous dehydration.

3. A 78-year-old woman with dementia has responded modestly to donepezil (Aricept, a cholinesterase inhibitor) for the past year. The recent onset of urge incontinence led her primary physician to prescribe tolterodine last month while awaiting your assessment. Her incontinence has responded well. The next appropriate step is which of the following?

- A. Discontinue tolterodine because of its interaction with donepezil.
- B. Discontinue donepezil because her cognitive function is stable.
- C. Discontinue both drugs because she is stable and the urge incontinence may reflect an adverse effect of the donepezil.
- D. Continue both drugs and monitor her for deterioration in cognitive function.
- E. Taper the tolterodine.

Answer: D Because cholinesterase inhibitors block the metabolism of acetylcholine, they can provoke urge incontinence, especially in older adults who already may have underlying age-related involuntary detrusor contractions that have not yet caused incontinence. However, despite prescription of these agents to millions of demented patients, there is little evidence that they cause incontinence. Moreover, because the benefits of these drugs for dementia are modest at best and not seen in most patients who use them, patients and families may decide that the benefit of the bladder relaxant outweighs the risk. Particularly in this patient, who has already benefited from tolterodine without notable cognitive deterioration, it is worth continuing therapy and monitoring her cognitive status.

4. A 53-year-old woman says that she has frequent leakage. It most commonly occurs about 10 seconds after she coughs or laughs. Having suffered for years, she is interested in the approach with the best chance of success.

- A. Pelvic muscle strengthening exercises (“Kegels”)
- B. An α -adrenergic agonist (e.g., pseudoephedrine)
- C. A pessary
- D. Urethral suspension surgery
- E. A bladder relaxant drug

Answer: E Most stress incontinence results from weakness of intrinsic sphincter muscle or pelvic muscle support. In all such cases, however, leakage coincides instantaneously with the increase in abdominal pressure and ceases as soon as the cough ends. In this case, however, there is a delay between the cough and leakage. This finding suggests that the cough has triggered an involuntary detrusor contraction, which then leads to leakage. Therapy should focus on reducing or eliminating the precipitant of coughing (e.g., bronchospasm, use of an angiotensin-converting enzyme inhibitor) or the underlying detrusor overactivity.

5. Which of the following is true of incontinence in demented elderly patients?

- A. Is inevitable
- B. Is virtually always due to detrusor overactivity/overactive bladder
- C. Is unlikely to respond to therapy
- D. Is multifactorial and often reversible
- E. Treatment should focus primarily on preventing skin breakdown

Answer: D Incontinence is never normal, even in patients with dementia. Detrusor overactivity is the most common type of lower urinary tract dysfunction among demented and incontinent nursing home residents, but it is also the most common dysfunction among their dry peers. Moreover, in 40% of these individuals, incontinence is not associated with detrusor overactivity but with obstruction (in men), stress incontinence (in women), or a combination of an outlet and a detrusor problem, and the cause does not correlate with either the presence or severity of dementia. Thus, it is not tenable to attribute incontinence *a priori* to detrusor overactivity. Because incontinence in elderly people is usually multifactorial, involving urinary tract as well as non-urinary tract contributions, it is often treatable. Even among nursing home patients, randomized studies of just a toileting regimen have shown more than a 50% reduction in incontinent episodes overall and full daytime continence in nearly 40% of residents. Because causes of transient incontinence are particularly common in demented individuals, additional benefit can be achieved by addressing other common contributors to their incontinence, including medication use, depression, fecal impaction, urinary tract infection, atrophic vaginitis, and disorders of fluid excretion. For those with detrusor overactivity, a bladder relaxant may provide additional help; for those with urethral obstruction or incompetence, minimally invasive procedures can be helpful. It is also important to prevent skin breakdown, but such treatment should not be the primary approach to the incontinent nursing home resident.

1. An 82-year-old woman with atrial fibrillation, congestive heart failure, hyperlipidemia, diabetes mellitus, and hypertension is brought to you by her daughter for evaluation of the acute onset of disorientation and agitation. Her medications include furosemide, metoprolol, atorvastatin, sertraline, warfarin, ranitidine, amlodipine, and an over-the-counter sleep remedy containing diphenhydramine. Which of her medications are *most likely* to be contributing to her altered mental status?

- A. Furosemide, metoprolol, and amlodipine
- B. Warfarin, atorvastatin, and sertraline
- C. Sertraline, ranitidine, and diphenhydramine
- D. Diphenhydramine, warfarin, and metoprolol
- E. Atorvastatin, furosemide, and sertraline

Answer: C Drugs with psychoactive side effects are most likely contributing to this patient's altered mental status. Anticholinergic drugs (such as diphenhydramine) are common contributors to mental status changes. Over-the-counter medications containing these agents should be used with caution in older persons. H₂-receptor blockers are among the most common drugs contributing to delirium. Antidepressants may also contribute to mental status changes, even at therapeutic levels. Choice A is not correct because these drugs are not highly correlated with mental status changes, although metoprolol can cross the blood-brain barrier. A major adverse effect of this combination in the elderly is orthostatic hypotension. All of the other combinations have only one drug listed that has marked psychoactive effects.

2. A 78-year-old man with hypertension, peripheral vascular disease, osteoarthritis of the knees, and macular degeneration is brought in by his daughter for evaluation of confusion and "failure to thrive" after a flu-like illness 2 months ago. The daughter reports that during the past few weeks, her father has been drowsy and sleeping most of the day. His memory is poor at times, but he remains independent in all self-care activities. Normally active, he has stopped his usual gardening and walking and shows little interest in interacting with his grandchildren, which he normally enjoys. His appetite is poor, and he has lost weight. Your examination reveals a flattened affect with poor eye contact. Neurologic examination is nonfocal without cogwheeling or tremor. On the Short Portable Mental Status Questionnaire, he has two errors after initially poor effort, which improved after extensive prompting and encouragement. He scores 7 of 15 on the Geriatric Depression Scale. What is the most likely diagnosis?

- A. Early-onset Parkinson disease
- B. Mild cognitive impairment
- C. Early dementia (combined vascular and Alzheimer type)
- D. Post-viral encephalitis
- E. Major depressive disorder

Answer: E This patient demonstrates symptoms of a major depressive disorder, including anhedonia, loss of interest in his usual activities, excessive sleep, loss of appetite, and weight loss. His cognitive screening test reveals cognitive "dilapidation" with poor effort, sometimes called a pseudodementia. His depression screening reveals marked depressive symptoms. In older persons, somatic symptoms are often more prominent than mood complaints. This patient should be referred for immediate geropsychiatric evaluation and management. Precipitants are not always present, but bereavement and acute or chronic medical conditions can contribute. There is no evidence of Parkinson disease, and the patient does not meet criteria for mild cognitive impairment or dementia.

3. Older persons are at least three times more likely than younger persons to experience an adverse drug reaction. All of the following contribute to this propensity *except* which one?

- A. Greater number of drugs
- B. Multiple chronic conditions
- C. Decreased glomerular filtration rate
- D. Decreased hepatic function
- E. Increased physiologic reserve

Answer: E Because of a greater number of drugs and chronic conditions, the elderly are at increased risk of drug-drug and drug-disease interactions. In addition, renal and hepatic functioning are relatively decreased, as is physiologic reserve capacity. Drug receptor sensitivity can be either increased or decreased, depending on the drug and receptor regulation.

4. An 86-year-old widowed woman living alone with peripheral vascular disease, lower extremity amputation, hypertension, and old stroke without residua is brought in by her neighbor for increasing forgetfulness during the past year. Your examination reveals a cheerful, interactive, and well-groomed woman with normal findings on neurologic examination. She has five errors on the Short Portable Mental Status Questionnaire. What is the most appropriate next step in her evaluation?

- A. Obtain brain imaging and lumbar puncture
- B. Assess her activities of daily living and level of independence
- C. Initiate treatment with an acetylcholinesterase inhibitor
- D. Initiate treatment with an antidepressant
- E. Refer her for nursing home placement

Answer: B Assessment of activities of daily living (both basic and instrumental) is key to the diagnosis of dementia, and information must often be obtained from a reliable informant. This is the important next step in the evaluation. Dementia can be diagnosed only in the presence of a functional impairment. After this assessment is complete, further evaluation can include laboratory work, neuroimaging, and other testing as required. Her ability to live independently must also be assessed, and social work involvement is recommended after a diagnosis is established.

Ch / 28 DELIRIUM OR ACUTE MENTAL STATUS CHANGE IN THE OLDER PATIENT

1. An 85-year-old woman with a history of hypertension, diabetes, transient ischemic attacks, prior cerebrovascular event without residua, hearing loss, and remote breast cancer is brought in to your office by her daughter for increasing memory lapses. The patient lives alone, but her daughter is nearby and very attentive. What would be the most appropriate next steps in the evaluation?

- A. Recent history and urgent brain MRI scan
- B. Recent history, cognitive screening, and neurologic examination
- C. Recent history, neurologic examination, and brain MRI scan
- D. Chest and head CT scans for metastatic disease
- E. Recent history, carotid ultrasound, and brain MRI scan

Answer: B The first step is to establish a diagnosis of the memory problem, which requires a history of the mental status change from the daughter, a careful neurologic examination for focal changes, and cognitive screening tests. If the changes are acute, with inattention and cognitive dysfunction on testing, delirium must be excluded. If the changes are chronic with memory impairment on cognitive testing, dementia is more likely. Neuroimaging tests would not be appropriate first steps in the evaluation.

2. You obtain the recent history and conduct cognitive screening of the patient in question 1. The daughter indicates to you that the patient has long-standing short-term memory problems but has been having more difficulty with her regular activities (like forgetting items at the grocery store and getting lost while driving) and has had episodes of disorientation during the past 1 to 2 weeks; at times, she has not made sense on the telephone. On your examination, you find that her neurologic examination is nonfocal, and she makes six errors on the Short Portable Mental Status Questionnaire. She has difficulty in following instructions and gives nonsense answers to some questions. She is disoriented to date, month, and year; she makes five errors on months of the year backwards. What are the key aspects of the history and evaluation that support a diagnosis of delirium?

- A. Disorientation, memory loss, and functional impairments (driving, shopping)
- B. Disorientation, memory loss, and inattention
- C. Acute onset, disorientation, memory loss
- D. Acute onset, inattention, and evidence of disorganized thinking
- E. Acute onset, inattention, and functional impairments (driving, shopping)

Answer: D The key features of a delirium include the acute onset, inattention (in this case manifested by her difficulty in following instructions and errors on the sustained attention task of months of the year backwards), and evidence of disorganized thinking (in this case manifested by the errors on the mental status questionnaire and her nonsense answers to questions). Acute onset of disorientation and the functional impairments are supportive features but not key diagnostic elements. The memory impairment has been chronic, so it is not helpful diagnostically in this case. Formal cognitive screening is key in establishing the diagnosis of delirium.

3. You are called as the medical consultant to evaluate JS, an 89-year-old retired accountant admitted to the urology service for removal of a benign ureteral tumor, because of a recent history of falling and weight loss. He is ready for discharge, but the family is concerned about his "failure to thrive." He has a history of chronic renal insufficiency, hypertension, intermittent atrial fibrillation, diastolic dysfunction, previous transient ischemic attacks, positive response to PPD, legal blindness due to macular degeneration, osteoarthritis, chronic reflux esophagitis, depression, and mild cognitive impairment. He smokes about three cigars per day and drinks two or three glasses of wine with dinner each evening. His current daily medications include aspirin, famotidine, paroxetine, metoprolol, amiodarone, amlodipine, naproxen, clopidogrel, and a multivitamin with minerals. He takes furosemide about three times a week for ankle edema. His daughter tells you that during the past month, his appetite has been poor in the context of severe heartburn, and he has become increasingly

withdrawn and refuses to eat. He has had two falls in the past week and one fall in the hospital last night. In addition, she has found him wandering and disoriented several times during the past week. On your examination, he has temporal wasting and bruised areas on his shoulders, but his neurologic examination is nonfocal. He is disoriented to place, date, day, and year; he makes three errors on serial sevens. He reports seeing butterflies on the bed. He is unable to cooperate with the full mental status testing, stating that he has to get to the bank immediately. What is the *most likely* factor contributing to this patient's delirium?

- A. Malnutrition and dehydration
- B. Postoperative status
- C. Multifactorial etiology
- D. Polypharmacy
- E. Multimorbidity and depression

Answer: C This is a classic example of delirium resulting from multifactorial etiology in an older person, that is, the complex interplay between baseline, predisposing (vulnerability) factors and precipitating (noxious) factors. Although each of the other answers is likely to be contributing to some degree, the fundamental principle is that delirium is typically of multifactorial etiology in the elderly.

4. You have completed your evaluation of JS (question 3) and made your recommendations to the urologist, including recommendations for a metabolic profile, which reveals a sodium level of 126 mg/dL. The urologist insists that the patient is ready to be discharged and recommends that any further evaluation be completed on an outpatient basis. What are the most appropriate management strategies for the patient at this point?

- A. Discharge from the hospital with completion of the evaluation on an outpatient basis by the primary care physician
- B. Discharge from the hospital with completion of evaluation on an outpatient basis by the geriatric assessment clinic
- C. Keep patient on the urology service and attempt to complete the evaluation and to institute a management plan
- D. Obtain a social work consultation for post-acute placement
- E. Transfer to the medical service to complete the evaluation and to institute a management plan

Answer: E Because delirium can be a medical emergency, it is important to complete the evaluation in the inpatient setting on a timely basis. Given the expertise needed, this goal may be best achieved on the medical service. The most important next steps are to ensure the patient's safety and to prevent further falls, to evaluate the patient for possible significant head trauma with neuroimaging, to correct hyponatremia and other metabolic derangements, to eliminate or to reduce nonessential psychoactive medications, and to provide appropriate hydration and nutrition. It would not be appropriate at this point to discharge the patient or to transfer him to a post-acute setting.

5. Before JS (case in question 3) was admitted for surgery, what were the *most appropriate* strategies that would have been helpful to prevent delirium?

- A. Treatment with oral low-dose haloperidol before, during, and for 3 days after surgery
- B. Treatment with oral olanzapine before surgery and sublingual olanzapine after surgery for 48 hours
- C. Treatment with donepezil beginning 2 to 4 weeks before surgery and continuing for 1 month postoperatively
- D. Multicomponent nonpharmacologic prevention strategies to address orientation, mobility, medications, vision and hearing impairments, nutrition, and hydration
- E. Interdisciplinary geriatric consultation beginning on the first postoperative day to address functional and cognitive status

Answer: D To date, there is no grade A evidence that any pharmacologic strategies are effective for preventing delirium. The current recommendation is to use multicomponent nonpharmacologic interventions to address delirium risk factors, such as the Hospital Elder Life Program (HELP) model (which allows fulfillment of all of the NICE guidelines for delirium prevention). Proactive delirium consultation is effective if it is started preoperatively.

1. A drug is considered to be effectively cleared from the circulation after how many half-lives?

- A. 1.5
- B. 2
- C. 5
- D. 7
- E. 10

Answer: C A drug is considered to be effectively cleared when less than 10% of drug remains in the circulation. This is typically 3 to 5 half-lives.

2. Which one of the following drugs may be difficult to remove in an overdose setting because of a large volume of distribution (VD)?

- A. Procainamide
- B. Aspirin
- C. Digoxin
- D. Phenobarbital
- E. Phenytoin

Answer: C A large VD indicates that a large fraction of the specific drug is present outside the circulation. Examination of drugs in Table 29-1 demonstrates that digoxin's VD is much higher than the other four drugs such that, in an overdose situation, easy removal of digoxin from the affected individual would be difficult because a large fraction of the drug is outside the circulation and therefore relatively inaccessible.

3. The antihistamine terfenadine (Seldane) should not be administered with which one of the following fruit juices?

- A. Lemon juice
- B. Orange juice
- C. Prune juice
- D. Grapefruit juice
- E. Apple juice

Answer: D Many drugs are metabolized by CYP3A4 in the small intestine. Certain chemicals in grapefruit juice, but not in the other juices listed, block the action of CYP3A4, so instead of being metabolized, more of the drug enters the blood stream and stays in the body longer. The result is that potentially dangerous levels of the drug accumulate. This finding has led to more attention to foods, herbs, and other natural substances that are coadministered with drugs.

4. Which one of the following drugs has pharmacokinetics characterized as dose-dependent, nonlinear saturation kinetics?

- A. Digoxin
- B. Tobramycin
- C. Lidocaine
- D. Glimepiride
- E. Phenytoin

Answer: E Not all drugs behave the same when drug dose is increased. The elimination of most drugs follows first-order or linear kinetics, such that the amount of drug eliminated is directly proportional to the plasma concentration of the drug. A few drugs (e.g., phenytoin) have a different pattern of elimination—that is, dose-dependent, nonlinear kinetics—such that as the drug dose increases and the plasma concentration of the drug rises, the relative amount of the drug being eliminated falls (i.e., clearance decreases) until the rate of drug metabolism is at a maximum. At this point, drug elimination is said to be zero order, and the drug concentration in plasma starts to increase much more (no longer linear). This is shown in Figure 29-5B.

5. Before administration of vemurafenib, which one of the following genes should be monitored for the presence of a V600E single-nucleotide polymorphism?

- A. EGFR
- B. BRAF
- C. NMYC
- D. VEGF
- E. CMYC

Answer: B The effectiveness of vemurafenib in tumors has been demonstrated to be dependent on the presence of a specific mutation in the *BRAF* gene of the tumor, a valine-to-glutamic acid mutation at residue 600 (V600E). This mutation results in the oncogene protein product, BRAF(V600E) kinase, exhibiting a markedly elevated activity that overactivates the MAPK signaling pathway. Vemurafenib selectively binds to the adenosine triphosphate-binding site of BRAF(V600E) kinase and inhibits its activity, resulting in inhibition of an overactivated MAPK signaling pathway downstream in BRAF(V600E) kinase-expressing tumor cells, thereby reducing tumor cell proliferation. Before considering this drug, specific testing for the presence of this mutation is recommended.

1. Which one of the following describes central neuropathic pain?

- A. A type of nociceptive pain
- B. Most often seen after a stroke
- C. A major cause of the pain of irritable bowel syndrome
- D. Almost never genetic in etiology
- E. Usually not responsive to anticonvulsants like gabapentin and pregabalin

Answer: B The most common overall cause of central pain is central post-stroke pain, occurring after about 8% of cerebrovascular accidents. Central pain and peripheral pain are the two major types of “neuropathic pain,” whereas “nociceptive pain” usually results from an injury or disease affecting somatic structures like skin, muscle, tendons, bone, joints, and ligaments. The pain of irritable bowel syndrome is one of the visceral forms of nociceptive pain (see Table 30-1). Gabapentin and pregabalin are considered first-line therapies for central neuropathic pain (see Table 30-3). Heritability is a component of practically all types of pain, including central neuropathic pain, estimated to account for between 30 and 60% of the variance in pain response (see Genetics). See Neuropathic, Nociceptive, and Mixed Pain.

2. Which of the following is true regarding diagnostic testing for pain?

- A. Imaging has little if any role in diagnosing the cause of pain.
- B. MRI findings correlate well with the intensity of spinal pain.
- C. Early imaging for back pain guides decision making and improves outcomes.
- D. Normal neurophysiologic (EMG, nerve conduction) test results are useful to rule out a neuropathic etiology of pain.
- E. MRI is ideal for discerning inflammation and soft tissue pathology as causes of pain.

Answer: E For nonspinal pain conditions, MRI is ideal for identifying inflammation and soft tissue pathology. (In contrast, CT scanning may be better for detecting bleeding and bone pathology as causes of pain.) There is poor correlation, however, between MRI findings and the intensity of spinal pain, with more than 50% of asymptomatic individuals having abnormalities on lumbar, thoracic, and cervical views. Systematic reviews have found that early imaging for back pain does not improve outcomes or affect decision making and should be reserved for those individuals with indications of a serious underlying condition (see reference A1). EMG and nerve conduction studies are associated with significant false-negative rates and are not sensitive in detecting impairment of small fiber conduction; therefore, normal results do not rule out neuropathic pain. See Diagnostic Tests.

3. Which of the following statements is true regarding opioid analgesics?

- A. Most opioids are devoid of end-organ toxicity.
- B. Opioids are comparably effective for long-term pain relief in cancer and noncancer patients.
- C. Opioids delivered by patient-controlled analgesia (PCA) require intensive supervision.
- D. Most patients on opioid therapy for chronic pain become addicted and/or abuse their drug.
- E. Opioids are cleared primarily by the liver, not the kidneys.

Answer: A Most opioids are not associated with end-organ toxicity, with the notable exception being meperidine. Abuse of drugs and addiction are potentially serious complications of long-term opioid use but are estimated to occur in only 20% and 10% of such individuals, respectively. Morphine is one of the opioids eliminated predominantly by the kidneys and should be used with caution in patients with renal dysfunction. Opioid analgesics are the cornerstone of treatment for cancer pain. In contrast, several recent reviews and guidelines have concluded that they provide long-term improvement in only a minority of individuals with noncancer pain conditions (see reference A10). PCA devices are safe; are programmed with basal infusion, bolus dose, lockout interval, and maximum dose per hour controls; and allow patients to control their pain management with less dependence on health care providers. See Opioid Analgesics.

Ch / 31 BIOLOGY OF ADDICTION

1. In addition to dopamine, all of following are important mediators of reward signals in the brain EXCEPT which?

- A. Acetylcholine
- B. Endocannabinoids
- C. Dynorphin
- D. Endorphins and enkephalins

Answer: C Dynorphin, although an endogenous opioid peptide, does not activate μ (mu) and δ (delta) opioid receptors. Rather, it activates κ (kappa) opioid receptors, which mediate an aversive effect. See reference 7.

2. Which of following brain regions is NOT important in controlling responses to rewarding stimuli in the environment?

- A. Amygdala
- B. Occipital cortex
- C. Hippocampus
- D. Prefrontal cortex
- E. Dorsal striatum

Answer: B All of the other brain regions listed are key components of the brain's reward circuitry. In contrast, the occipital cortex is most important for detecting and interpreting visual stimuli. See reference 7.

3. Which of the following statements best describes the activity of dopamine neurons in the ventral tegmental area in response to rewards?

- A. The neurons show large increases in phasic firing in response to an unexpected reward.
- B. The neurons show large increases in phasic firing in response to the withholding of an expected reward.
- C. The neurons show large increases in tonic firing in response to the withholding of an expected reward.
- D. The neurons show large decreases in tonic firing in response to an unexpected reward.

Answer: A Unexpected rewards induce an increase in phasic firing of the neurons. All other answers are incorrect responses. See reference 7.

4. Which of the following properties is unique to a drug of abuse?

- A. It increases dopamine signaling from the ventral tegmental area to the nucleus accumbens.
- B. It increases dopamine signaling from the substantia nigra to the dorsal striatum.
- C. It decreases dopamine signaling from the substantia nigra to the dorsal striatum.
- D. Its repeated use is associated with tolerance.
- E. Its repeated use is associated with dependence and withdrawal.

Answer: A All drugs of abuse share only one property: increasing dopamine transmission from the ventral tegmental area to the nucleus accumbens. Choices B and C are incorrect. Although drugs of abuse do cause tolerance and dependence/withdrawal (choices D and E), many nonabused drugs do so as well. See reference 7.

5. Which of the following is NOT a known mechanism of a drug of abuse?

- A. Cannabinoid receptor agonist
- B. Nicotinic cholinergic receptor agonist
- C. NMDA glutamate receptor antagonist
- D. GABAA receptor agonist
- E. Dopamine receptor antagonist

Answer: E All drugs of abuse increase dopamine signaling; a dopamine receptor antagonist would block some of the actions of a drug of abuse. All other answers are known mechanisms of a drug of abuse. See reference 7.

Ch / 32 NICOTINE AND TOBACCO

1. Which of the following is the level of reduction in smoking that is associated with significant lowering of cardiovascular and respiratory disease risk?

- A. 25%
- B. 50%
- C. 75%
- D. 100%

Answer: D See Epidemiology section.

2. Which of the following signs and symptoms is NOT associated with nicotine withdrawal?

- A. Irritability
- B. Insomnia
- C. Weight gain
- D. Gastrointestinal discomfort

Answer: D See Diagnosis section.

3. Polymorphisms in the following genes have been associated with successful smoking cessation outcomes, EXCEPT which gene?

- A. CHRNA4
- B. Neuregulin
- C. COMT
- D. CHRNA3

Answer: B See Prognosis section.

4. Which of the following is NOT an evidence-based behavioral interventions for smoking cessation?

- A. Cognitive behavioral therapy (CBT)
- B. Motivational interviewing
- C. Dialectical behavioral therapy (DBT)
- D. Brief interventions

Answer: C See Table 32-1.

5. Which of the following medications may be effective as adjunctive treatment to behavioral therapies for smoking cessation?

- A. Naltrexone
- B. Nicotine vaccine
- C. Mecamylamine
- D. Nortriptyline

Answer: D See Table 32-2.

Ch / 33 ALCOHOL USE DISORDERS

1. A 58-year-old man presents to his primary care physician's office for follow-up of hypertension. During the visit, he reports that he consumes 3 to 4 glasses (approximately 5 ounces each) of red wine every day but denies any medical, behavioral, or social problems related to his drinking. He is a nonsmoker and does not have a history of alcohol or other substance use disorders. On examination, his blood pressure is 144/96 mm Hg, his pulse is 80 beats per minute, and the remainder of his examination is unremarkable. What would be the most appropriate next step concerning his alcohol consumption?
- A. Refer him to Alcoholics Anonymous.
 - B. Suggest that his current red wine consumption might have health benefits, but he should not drink more than this amount.
 - C. Prescribe naltrexone to help him stop drinking.
 - D. Refer him to an alcohol treatment program for counseling.
 - E. Advise him to decrease his consumption to no more than 2 drinks a day and reassess his alcohol use at the next visit.

Answer: E This patient exhibits “at-risk” drinking—a level of alcohol consumption that increases his risk for alcohol-related health or social problems. Randomized clinical trials have demonstrated that brief physician advice in a primary care setting can result in reduced alcohol consumption, often to levels that are below those considered to be of risk in a patient such as this (e.g., ≤ 2 drinks/day). In this patient's case, decreasing his alcohol use may also improve his blood pressure control. The health-related risks associated with this level of alcohol consumption are likely to far outweigh any potential (and likely minimal if any) benefit from consumption of red wine. Alcoholics Anonymous, naltrexone, and referral to an alcohol treatment program for counseling should be considered in patients who meet criteria for an alcohol use disorder, which is not the case with this patient.

2. A 30-year-old woman presents for evaluation of “shakiness.” She reports several months' history of heavy alcohol consumption, typically 8 to 10 drinks per day including wine and vodka. Her presenting complaint began when she decided to quit drinking 1 day ago because she was recently placed on probation at work because of frequent tardiness related to her alcohol use. She notes that she has been drinking increased amounts of alcohol to “keep going” and that when she does try to decrease her alcohol use, especially with her recent trouble at work and some “close calls” while driving, she is unsuccessful. Which of the following best describes her alcohol consumption pattern and its related effects?
- A. She is suffering from alcohol-related delirium tremens.
 - B. She has a severe alcohol use disorder.
 - C. She meets criteria for alcohol abuse.
 - D. She has a mild alcohol use disorder.
 - E. She is not a binge drinker.

Answer: B This patient meets at least six of the DSM-5 criteria for an alcohol use disorder and thus would be considered in the severe category. Her presentation as described includes several of these criteria: evidence of tolerance, withdrawal, more use than intended, unsuccessful attempts to cut down, tolerance, use despite negative effects, failure to fulfill a major role obligation, and use in hazardous situations. Although she does present with symptoms likely related to alcohol withdrawal, there is nothing in the presentation to suggest delirium tremens. *Alcohol abuse* is a term from earlier versions of DSM and is no longer used as diagnosis. Patients with a “mild” alcohol use disorder have only two or three of the DSM-5 criteria. She does not meet criteria for binge drinking.

3. The same 30-year-old woman described in question 2 eventually develops severe enough withdrawal symptoms to be hospitalized for the medical management of her alcohol withdrawal. Which of the following is true concerning the course of her alcohol withdrawal?

- A. If present, withdrawal seizures are likely to occur between 48 and 72 hours after the last drink.
- B. Chlordiazepoxide and diazepam are the only benzodiazepines that have been approved by the FDA for the treatment of alcohol withdrawal.
- C. Benzodiazepines have been demonstrated to effectively reduce the occurrence of alcohol withdrawal seizures.
- D. Longer acting benzodiazepines are always preferred to those that are shorter acting.
- E. β -Blockers are an effective alternative to benzodiazepines for the treatment of alcohol withdrawal.

Answer: C Benzodiazepines are the treatment of choice for the alcohol withdrawal syndrome. There is strong evidence that they decrease the frequency of alcohol withdrawal seizures, and numerous randomized trials have demonstrated their effectiveness in controlling withdrawal-related symptoms and vital sign abnormalities. Alcohol withdrawal seizures tend to occur within 12 to 24 hours after alcohol consumption is reduced or stopped. There are four benzodiazepines that have been approved by the FDA—in addition to the two mentioned in choice B, oxazepam and lorazepam are also FDA approved. Short-acting benzodiazepines may be preferred in patients with severe liver disease. β -Blockers are effective adjuncts to benzodiazepines in the treatment of alcohol withdrawal but should not be used alone as an alternative to benzodiazepines.

4. The same 30-year-old patient presented in questions 2 and 3 is discharged from the hospital after successful treatment of the alcohol withdrawal syndrome. Which of the following is the appropriate “next step” in the management of her alcohol-use disorder?

- A. Assess her motivation to remain alcohol free and determine her interest in receiving treatment for relapse prevention.
- B. Refer her to the Alcoholics Anonymous program that your father went to.
- C. Continue her benzodiazepines as an outpatient to help her stay away from alcohol.
- D. Discharge her on disulfiram and see her back in your office in a month.
- E. Advise her to abstain from alcohol and see her back in your office in a month.

Answer: A The first step in managing patients with alcohol use disorders who have been successfully detoxified is to assess their motivation to remain alcohol free and discuss various follow-up treatment options in order to assess their interest in treatment and help identify the best approach to getting relapse prevention therapy. Patients who are suitably motivated and interested in engaging in ongoing treatment should then be referred as appropriate. Those who are not ready to accept treatment may benefit from motivational interviewing approaches and close follow-up in order to engage them in treatment in the future. Alcoholics Anonymous may be helpful to many patients; however, without assessing a patient’s motivation, it is difficult to tell if such a referral will be followed. In addition, AA meetings differ in terms of their content and membership, and patients may need to try several meeting sites to find a group that they are comfortable with. Benzodiazepines are not indicated for the prevention of relapse to alcohol use. Disulfiram has been shown to be effective in highly motivated patients who receive treatment in a highly supervised manner. There is no evidence that brief advice alone is effective in the treatment of alcohol use disorders.

5. A 47-year-old man presents to his primary care physician for a routine preventive health visit. He has a history of an alcohol use disorder and has been hospitalized three times for alcohol withdrawal, is participating in Alcoholics Anonymous, and is currently getting cognitive behavioral therapy from a therapist. Despite this, he continues to struggle with craving for alcohol and has had numerous relapses interrupting episodes of sobriety. He has heard about medications that might help him prevent these relapses and would like to try something. Which of the following is the most appropriate recommendation?

- A. Don’t use a relapse prevention medication because this will be frowned upon by his Alcoholics Anonymous group.
- B. Give him a prescription for disulfiram and ask him to follow up in 3 months.
- C. Start with a combination of naltrexone and acamprosate because this will yield the best results.

D. Consider the use of intramuscular naltrexone, 380 mg per month.

E. Prescribe topiramate, 300 mg a day.

Answer: D In several clinical trials, naltrexone has been demonstrated to decrease alcohol consumption in individuals who are dependent on alcohol. Although generally well tolerated, contraindications include current opioid dependence and severe liver disease. Although it is true that some Alcoholics Anonymous participants or groups may frown upon the use of medication to treat alcohol use disorders, this is not a reason to not use these medications. However, patients should be made aware of this possibility and counseled on how to deal with this if it occurs. Disulfiram has been shown to be effective in highly structured treatment programs. Although it may be helpful in some primary care patients, there is no evidence that it is effective when used by primary care physicians in an unstructured manner. There is no significant evidence that combinations of relapse prevention medications improve outcomes in patients who are dependent on alcohol. Topiramate has been demonstrated to be effective in preventing relapse to alcohol use in some studies, but it is not yet approved for this indication.

1. Which of the following substances is NOT associated with withdrawal seizures?

- A. Cocaine
- B. Alprazolam
- C. Butalbital
- D. Alcohol
- E. Chlordiazepoxide

Answer: A Cocaine causes a seizure upon intoxication, not withdrawal. Sedative-hypnotic agents cause withdrawal seizures.

2. Which of the following symptoms is seen as a result of opioid withdrawal?

- A. Grand mal seizure
- B. Miosis
- C. Constipation
- D. Tachycardia
- E. Synesthesia

Answer: D Miosis and constipation occur with intoxication, seizures are not seen with opioid withdrawal, and synesthesia (seeing sounds, hearing colors) is seen in hallucinogen intoxication.

3. Which of the following symptoms does NOT count as a symptom of a substance use disorder?

- A. Physical dependence in a patient taking opioids as prescribed for pain
- B. Craving
- C. Taking more than intended
- D. Use despite family problems
- E. Persistent desire to cut down on drug use

Answer: A Physical dependence and tolerance are not considered criteria for a substance use disorder if they occur as a result of appropriate medical care.

4. Which of the following is NOT an FDA-approved medication for treatment of opioid dependence?

- A. Acamprosate
- B. Oral naltrexone
- C. Extended-release injectable naltrexone
- D. Methadone
- E. Sublingual buprenorphine

Answer: A Acamprosate is approved for the treatment of alcohol use disorders; the other medications are approved for the treatment of opioid dependence.

5. Other than marijuana, what type of drug is most widely abused?

- A. Prescription drugs
- B. Hallucinogens
- C. Cocaine
- D. Methamphetamine
- E. Heroin

Answer: A Prescription drugs, especially opioids, are much more widely used nonmedically than the other drugs of abuse.

Ch / 36 BIOLOGIC AGENTS AND SIGNALING INHIBITORS

1. Which of the following TNF inhibitors has not shown efficacy in Crohn disease?

- A. Infliximab
- B. Adalimumab
- C. Golimumab
- D. Etanercept

Answer: D The monoclonal anti-TNF antibodies (A, B, and C) reduce disease activity and requirement for glucocorticoid therapy in Crohn disease. Etanercept is a fusion protein containing the extracellular portion of TNF-R75 coupled to the Fc domain of IgG1. In addition to binding TNF, it also binds lymphotoxin- α . For reasons that are not clarified, etanercept has not been efficacious in inflammatory bowel disease.

2. Previous or current infection with which one of the following microbial organisms should be assessed before initiating anti-TNF therapy?:

- A. Meningococcus
- B. Mycobacterium tuberculosis
- C. Mycoplasma
- D. Histoplasmosis

Answer: B Anti-TNF therapy has been associated with increased risk for reactivation of latent tuberculosis. Patients should be evaluated and appropriately treated for presence of tuberculosis infection before initiation of anti-TNF therapy. Although histoplasmosis has occasionally occurred in patients treated with anti-TNF agents, testing for infection with this organism is not routinely performed before initiating therapy.

3. A monoclonal antibody that inhibits the biologic activities of IL-12 and IL-23 has shown efficacy in which of the following diseases?

- A. Psoriasis
- B. Crohn disease
- C. Systemic lupus erythematosus (SLE)
- D. A and B
- E. A, B, and C

Answer: D Ustekinumab has shown positive efficacy in trials in patients with psoriasis or Crohn disease. Although this agent might have potential use in SLE, data from clinical trials are not available.

4. Imatinib mesylate, a kinase inhibitor that has changed the prognosis of patients with chronic myelogenous leukemia, is also approved for which of the following diseases?

- A. Scleroderma
- B. Idiopathic pulmonary fibrosis
- C. C-Kit-positive advanced gastrointestinal tumor
- D. Rheumatoid arthritis
- E. Inflammatory bowel disease

Answer: C Imatinib mesylate (Gleevec) has antifibrotic activity in some murine models, providing rationale for testing this agent in diseases such as scleroderma or idiopathic pulmonary fibrosis. However, randomized controlled clinical trials of this agent have not been performed in those diseases at this time.

5. Blockade of costimulatory signals between CD28 and CD80/86 has led to approval of abatacept in which of the following diseases?

- A. Rheumatoid arthritis
- B. Chronic myelogenous leukemia
- C. Lupus nephritis
- D. Crohn disease

Answer: A Abatacept (Orencia) has shown efficacy in rheumatoid arthritis, as well as a related disease in children, polyarticular juvenile idiopathic arthritis. Despite a strong rationale for costimulatory blockade in SLE, trials of this agent were not effective in lupus nephritis nor in those with non-nephritic manifestations. Crohn disease can be treated with an agent that blocks migration of T cells, natalizumab. Chronic myelogenous leukemia has a different molecular pathophysiology and is effectively targeted by specific tyrosine kinase inhibitors.

Ch / 37 PROSTANOIDS, ASPIRIN, AND RELATED COMPOUNDS

1. The concomitant administration of which of the following drugs can interfere with the antiplatelet effect of low-dose aspirin?

- A. All traditional nonsteroidal anti-inflammatory drugs (NSAIDs)
- B. Celecoxib
- C. Ibuprofen and naproxen
- D. Acetaminophen
- E. Diclofenac

Answer: C Ibuprofen and naproxen are somewhat more potent in inhibiting COX-1 than COX-2 (as shown in Fig. 37-2) and can compete with aspirin for binding to a common docking site within the COX-1 channel, thereby interfering with permanent acetylation of the platelet enzyme. Other COX inhibitors that have some degree of COX-2 selectivity, such as celecoxib, acetaminophen, and diclofenac, do not display this pharmacodynamic interaction.

2. Which of the following is true regarding the increased risk for major vascular events associated with the use of COX-2 inhibitors?

- A. The increased risk is restricted to coxibs.
- B. The increased risk is shared by all NSAIDs.
- C. The increased risk is related to COX-2 selectivity.
- D. The increased risk is shared by NSAIDs that do not adequately inhibit platelet COX-1 activity.
- E. The increased risk requires a treatment duration of at least 18 months.

Answer: D Coxibs and traditional NSAIDs that do not adequately inhibit platelet COX-1 activity (e.g., diclofenac and ibuprofen) similarly increase the risk for major vascular events, regardless of their variable COX-2 selectivity. The increased risk appears early and does not require prolonged exposure. See reference A6.

3. The main features of the antithrombotic effect of low-dose aspirin include which of the following?

- A. Saturability of the effect at low doses
- B. A lowest effective daily dose in the range of 160 to 325 mg
- C. Differential effects in men versus women
- D. Differential effects in older versus younger subjects
- E. None of the above

Answer: A As indicated in Table 37-1, the lowest effective daily dose is in the range of 50 to 162 mg. The antithrombotic effect of aspirin is saturable at such low doses, inasmuch as higher doses were tested and not found to confer any greater risk reduction. The effect is similar in men and women, as well as in subjects younger and older than 65 years.

4. Prostaglandin H synthases do which of the following?

- A. Catalyze the conversion of PGH₂ to PGE₂
- B. Catalyze the first committed step in prostanoid biosynthesis from arachidonic acid
- C. Catalyze the release of arachidonic acid from membrane phospholipids
- D. Are inhibited irreversibly by all NSAIDs
- E. None of the above

Answer: B As shown in Figure 37-1, prostaglandin H synthases catalyze the conversion of arachidonic acid to PGG₂ and its reduction to PGH₂, that is, the first committed step in prostanoid biosynthesis. Other enzymes catalyze the release of arachidonic acid from membrane phospholipids and the conversion PGH₂ to PGE₂. Aspirin, but not other NSAIDs, inhibits prostaglandin H synthases irreversibly.

5. Which of the following is true of low-dose aspirin and traditional NSAIDs?

- A. They share the same molecular mechanism of permanent inactivation of COX-isozymes.
- B. They share the same pharmacologic effects.
- C. They differentially inhibit platelet COX-1 activity as a function of their mechanism of action and half-life.
- D. They have the same cardiovascular effects.
- E. None of the above

Answer: C As shown in Figure 37-3, low-dose aspirin and a traditional NSAID with a short half-life (e.g., ibuprofen) differentially inhibit platelet COX-1 activity during the dosing interval because of the irreversible versus reversible mechanism of action. Aspirin is primarily an antiplatelet agent at low doses administered once daily and requires higher doses and more frequent dosing to produce the same pharmacologic effects of traditional NSAIDs. The cardioprotective effects of low-dose aspirin are not shared by traditional NSAIDs.

Ch / 38 ANTITHROMBOTIC THERAPY

1. Based on the half-life and onset of action of warfarin, which of the following is the optimal management of this drug in the case of uncomplicated major surgery?
- A. Warfarin should be stopped 5 days before surgery and restarted as soon as the patient can take oral medications after surgery.
 - B. Warfarin should be stopped 2 days before surgery and restarted as soon as the patient can take oral medications after surgery.
 - C. Warfarin should be stopped 5 days before surgery and restarted at least 5 days after surgery.
 - D. Warfarin should be stopped 2 days before surgery and restarted at least 5 days after surgery.

Answer: A With a half-life of 40 hours, warfarin has to be stopped 5 days before surgery to eliminate the anticoagulant effect. It takes 5 to 7 days for warfarin to achieve therapeutic anticoagulant effect, and thus it can be started very shortly after surgery provided that there is no bowel paralysis or active bleeding. (Douketis JD, Spyropoulos AC, Spencer FA, et al. *Chest*. 2012;141:e326S-e350S.)

2. For a patient requiring treatment for pulmonary embolism but with a high risk for bleeding, for whom quick elimination of the anticoagulant effect is desirable, which one of the heparins is preferable?
- A. Unfractionated heparin (as intravenous infusion)
 - B. Fondaparinux
 - C. Danaparoid
 - D. Low-molecular-weight heparin

Answer: A With a half-life of 1 hour at therapeutic concentration, unfractionated heparin is the heparin that will be eliminated fastest. Low-molecular-weight heparins have half-lives of 2 to 3 hours, and fondaparinux and danaparoid about 20 hours.

3. For which one of the new oral anticoagulants would screening with a thrombin time analysis be sensitive to identify clinically important plasma concentrations of the drug?
- A. Dabigatran
 - B. Rivaroxaban
 - C. Apixaban
 - D. Edoxaban
 - E. Argatroban

Answer: A Dabigatran and argatroban are direct thrombin inhibitors, for which a thrombin time is a sensitive test, but argatroban is not an orally available drug. The others are factor Xa inhibitors, for which thrombin time is less sensitive.

4. Which combinations of antiplatelet therapy are recommended because they provide better effect than single-antiplatelet therapy?
- A. Aspirin + dipyridamole in noncardioembolic stroke and aspirin + clopidogrel in unstable angina/non-ST elevation myocardial infarction.
 - B. Aspirin + clopidogrel in noncardioembolic stroke and ticagrelor + clopidogrel in unstable angina/non-ST elevation myocardial infarction.
 - C. Aspirin + dipyridamole in noncardioembolic stroke and aspirin + clopidogrel in peripheral arterial disease.
 - D. Aspirin + dipyridamole in peripheral arterial disease and aspirin + ticagrelor in unstable angina/non-ST elevation myocardial infarction.
 - E. Aspirin + clopidogrel in peripheral arterial disease and aspirin + dipyridamole in cardioembolic stroke.

Answer: A In noncardioembolic stroke, aspirin plus dipyridamole provides a 37% reduction of recurrent stroke compared with 16% with dipyridamole alone. In unstable angina and non-ST elevation

myocardial infarction, the combination of aspirin plus clopidogrel provides 20% greater risk reduction than aspirin alone.

5. What is the objective of thrombolytic therapy in patients with acute ischemic stroke (treatment within 3 hours from onset of symptoms)?

- A. To improve the functional outcome
- B. To reduce mortality
- C. To reduce cardiovascular death
- D. To eliminate the need for anticoagulation
- E. To shorten the duration of hospitalization

Answer: A Treatment with tissue plasminogen activator within 3 hours of ischemic stroke is associated with a significant increase in the proportion of patients with good functional outcome. Even if duration of hospitalization may thereby be shortened, this is not the objective of the treatment. Thrombolysis does not reduce mortality and does not eliminate the need for ensuing anticoagulation in case of cardioembolic stroke.

Ch / 40 PRINCIPLES OF GENETICS

1. A couple have a child with autism spectrum disorder in whom chromosomal analysis has been done and was normal. Which of the following is recommended to search for a possible genetic cause?

- A. Cytogenomic microarray testing
- B. Fluorescence in situ hybridization
- C. High-resolution chromosome banding
- D. Whole exome sequencing
- E. Whole genome sequencing

Answer: A Cytogenomic microarray testing now can detect small copy-number changes (deletions or duplications) that would not be detected by standard cytogenetic analysis, including high-resolution banding.

2. A man has a direct-to-consumer genomic test and is found to have a 1.2 increased odds of type 2 diabetes. The basis for this testing is which of the following?

- A. Sequencing a gene known to be involved in type 2 diabetes
- B. Single-nucleotide polymorphism genotyping
- C. Analysis of RNA sequences in a saliva sample
- D. Whole exome sequencing
- E. Whole genome sequencing

Answer: B Direct-to-consumer genomic testing is currently based on genotyping of a large number of single nucleotide polymorphisms. (See Population Studies.)

3. A woman requests genetic testing for risk for breast cancer. Which of the following would constitute a risk factor for familial breast and ovarian cancer?

- A. History of tobacco use
- B. Sister with breast cancer diagnosed at 40 years of age
- C. Mother with ovarian cancer diagnosed at 80 years of age
- D. Father with history of lung cancer
- E. Maternal uncle with colon cancer

Answer: B A first-degree relative with early-onset breast cancer would constitute a risk factor for hereditary breast and ovarian cancer. (See Breast Cancer under Role of the Physician.)

4. A 40-year-old patient with Marfan syndrome seeks advice regarding medical surveillance. Which of the following represents the greatest health risk that may be subject to medical intervention?

- A. Dislocation of joints
- B. Dislocation of lens
- C. Aortic root dilation
- D. Cardiomyopathy
- E. Skin laceration

Answer: C Aortic root dilation and risk for aortic dissection are the most important life-threatening risks for individuals with Marfan syndrome and are subject to monitoring and intervention. (See Role of the Nonspecialist.)

Ch / 41 GENE, GENOMIC, AND CHROMOSOMAL DISORDERS

1. Which of the following genic regions is protein coding, i.e., translated into a polypeptide?

- A. Introns
- B. Micro-RNAs
- C. Small nucleolar RNAs
- D. Long noncoding RNAs
- E. Exons

Answer: E Only 1 to 2% of the genome consists of sequences that encode proteins. These protein-coding genic regions have exons and introns that are transcribed into messenger RNA (mRNA). However, only the exonic regions code for the amino acid sequences in the protein, and thus, the intervening intronic sequences are spliced out from the mature mRNA before translation. Micro-RNAs, small nucleolar RNAs, and long noncoding RNAs are transcribed but not translated; nevertheless, they are involved in many important biologic processes. (See Gene.)

2. Which of the following genetic variations in humans involves a change in a single base pair?

- A. Copy-number variants
- B. Single nucleotide polymorphism (SNP)
- C. Inversion
- D. Microsatellite
- E. Repetitive element

Answer: B Genetic diversity in humans can be due to variations in single nucleotides (e.g., SNP), copy-number (e.g., duplications, triplications), copy-neutral changes (e.g., inversions, absence of heterozygosity), microsatellites (e.g., short tandem repeats), and repetitive elements. Single nucleotide changes that have allelic frequency of more than 1% are termed *single nucleotide polymorphisms*. These SNPs have been used in association studies that have tried to assess whether particular alleles confer a higher risk for common disorders like diabetes. (See Genetic and Genomic Variation in Humans.)

3. Which of these diagnostic techniques cannot be used to detect deletions or duplications involving one or more genes?

- A. Sanger sequencing of genomic region of interest
- B. Array comparative genomic hybridization (aCGH)
- C. Multiplex ligation-dependent probe amplification (MLPA)
- D. Fluorescence in situ hybridization (FISH)
- E. SNP array

Answer: A Copy-number variations that include deletions or duplications can cause many human phenotypes. Sanger sequencing that involves amplification of specific regions of the genome followed by reading of the sequence typically cannot detect such copy-number changes. Molecular cytogenetic techniques that assess copy-number such as aCGH and SNP arrays (at the whole genome level) or FISH and MLPA (at specific regions of interest) should be employed in diagnosis of such deletions or duplications. (See Assaying Genetic Variation).

4. Two sisters and their brother who are affected with a severe form of neurologic disease presenting with structural brain malformation, intellectual disability, and behavioral abnormalities are evaluated for a genetic diagnosis. The parents and another sibling are asymptomatic and have no medical problems. A detailed family history shows no other members affected with a similar condition. Physical examination, laboratory tests, and imaging techniques do not point to any specific diagnosis. Which of these testing modalities is likely to be most useful in evaluation of this family?

- A. Array comparative genomic hybridization (aCGH)
- B. SNP array
- C. Whole exome sequencing (WES)
- D. Assaying for unstable repeat expansion
- E. High-resolution G-banded karyotyping

Answer: C Multiple affected individuals in the same generation without other family members being affected is most suggestive of an autosomal recessive disease. When the clinical phenotype is not distinct to narrow down the putative genes, WES is the diagnostic test most likely to provide a molecular confirmation. (See Assaying Genetic Variation).

5. A 50-year-old man presents with early-onset diabetes, hearing loss, muscle weakness, and stroke-like episodes. His brother, mother, two maternal uncles, maternal grandmother, and others have a history of a similar condition. Review of the extended pedigree shows no male-to-progeny transmission. With which molecular mechanism would this be most consistent?

- A. Autosomal dominant mutation that results in haploinsufficiency
- B. Autosomal dominant mutation that confers neomorphic property
- C. Autosomal dominant mutation that confers antimorphic property
- D. Mitochondrial DNA mutation
- E. Copy-number variants

Answer: D Whereas all the mutations mentioned can present with multiple members across generations being affected, the transmission of disease to progeny only through females is classic for mitochondrial DNA mutations. The phenotypic manifestations in individuals can vary based on the load of mutant mitochondrial DNA (heteroplasmy). (See Patterns of Inheritance.)

Ch / 42 THE INHERITED BASIS OF COMMON DISEASES

1. For most common diseases, concordance in disease status is higher in monozygotic twins than in dizygotic twins. This is an example of which phenomenon?

- A. Heritability
- B. Heterozygosity
- C. Epistasis
- D. Phenocopy

Answer: A Heritability is the fraction of interindividual variability in disease risk attributable to additive genetic influences. The contribution of shared genotype to a disease can be dissected further by comparing rates of disease within families as a function of the extent of genetic relatedness. The cleanest such design involves the comparison of disease concordance among dizygotic and monozygotic twin pairs. For common diseases such as types 1 and 2 diabetes mellitus, obesity, hypertension, coronary artery disease, autoimmune diseases, common cancers, schizophrenia, and bipolar disease, twin studies have documented that rates of concordance are significantly higher in monozygotic than in dizygotic twin pairs.

2. Heterozygosity is defined as the proportion of sites on the chromosome at which two randomly chosen copies differ in DNA sequence. Most heterozygosity in humans is due to

- A. Mutations common in frequency ($>1\%$)
- B. Rare mutations ($<1\%$)
- C. Mutations private to specific individuals
- D. Mutations that lead to loss of protein function

Answer: A The genetic variation in each of us is due largely to common variants. Empirically, more than 98% of the heterozygous sites in each individual display frequency of greater than 1% in the worldwide human population.

3. In cases in which a single gene is necessary and sufficient to cause disease, the condition is termed

- A. Mendelian disorder
- B. Polygenic condition
- C. Phenocopy
- D. Allelic heterogeneity
- E. Locus heterogeneity

Answer: A In cases in which a single gene is necessary and sufficient to cause disease, the condition is termed a mendelian disorder because the disease tracks perfectly with a mutation (in the family) that obeys Mendel's simple laws of inheritance.

4. Whereas a P value threshold of .05 is considered statistically significant in most of medicine, genome-wide association studies use a P value threshold of $<10^{-7}$ as "genome-wide significance." The principal reason for the more stringent statistical threshold in genome-wide association studies is to

- A. Account for multiple testing
- B. Account for population stratification
- C. Account for potential mismatching of cases and controls
- D. Account for technical artifacts

Answer: A Each genome contains millions of genetic variants, and presumably only a small fraction of these influence disease. This is often described as a problem of "multiple hypothesis testing," with the investigative community searching for associations between multiple genes, multiple variants in each gene, and multiple diseases. As a result, much more stringent statistical thresholds (than the traditional $P < .05$) are required for declaring association of genetic variants and disease, and typically $P < 10^{-7}$ is used.

5. Most variants associated with common diseases from genome-wide association studies are of which type?

- A. Noncoding variants
- B. Missense mutations
- C. Loss-of-function mutations
- D. Insertion-deletion polymorphisms in coding sequence

Answer: A Most of the associated single-nucleotide polymorphisms from genome-wide association studies lie in noncoding regions, suggesting that they act through effects on gene regulation rather than directly altering protein-coding sequences.

Ch / 43 APPLICATION OF MOLECULAR TECHNOLOGIES TO CLINICAL MEDICINE

1. Genome sequencing of DNA can be used for all of the following *except which one?*

- A. Diagnosis of rare diseases
- B. Detection of pharmacogenetic variants
- C. Newborn screening
- D. Prognosis of cancer
- E. Diagnosis of infection

Answer: D Various types of genome sequencing have served special clinical functions. Exome sequencing is being increasingly used to diagnose rare genetic diseases and patients with diagnostic dilemmas. Germline genotyping has allowed prediction of adverse events and dosing of many commonly used drugs; although these discoveries have been “actionable,” most have failed to diffuse widely into clinical practice at this time. Screening newborns, prenatal diagnosis, and preconception carrier testing are feasible for identified mendelian disorders. In infectious diseases, diagnosis of causative pathogens can be performed by next-generation sequencing, which may in the future supplant the need to first grow microorganisms in culture. Genome sequencing has not been demonstrated to be useful for prognosis of cancer at this time.

2. Transcriptional (RNA) profiling may be useful for all of the following *except which one?*

- A. Susceptibility
- B. Diagnosis
- C. Prognosis
- D. Pharmacogenetics
- E. Monitoring

Answer: A Next-generation sequencing has allowed sequencing of RNA transcripts in cells. The so-called transcriptome, unlike the static genome, is continually changing. It allows examination, at any given time, of alternatively gene-spliced transcripts, post-transcriptional changes, gene fusion, and changes in gene expression. Transcriptional (RNA) profiling has been applied to diagnosis, prognosis, pharmacogenomics, and monitoring, but not susceptibility analysis.

3. Among the great challenges to implementing genomic diagnostics in the clinic is which one of the following?

- A. The precision of the results
- B. The evidence to support use
- C. The ability of the laboratories to perform the test
- D. Their integration into electronic medical records
- E. Lack of patient understanding

Answer: B Surmountable challenges to implementing genomic diagnostics at the bedside include increasing the precision of results, expanding the availability of expert laboratories to perform the tests, the ability to integrate the information into electronic medical records, and lack of understanding by patients who are, however, now becoming increasingly savvy about this aspect of their own health care. Evidence to support the utility and cost-effectiveness of wide application of genomic diagnostics in clinical practice is only now being taken up by investigators in comparative effectiveness and health services research.

4. Which of the following describes the microbiome?

- A. A small genome
- B. A community of microbes colonizing humans
- C. A tool used to make thinly sliced materials (e.g., paraffin blocks)
- D. The sequence of a virus or bacterium
- E. An organelle of the cell

Answer: B The microbiome is the community of microbes that colonize a human host. It is the ecological community of commensal, symbiotic, and pathogenic microorganisms that actually inhabit our body space and outnumber our own native human cells by a ratio of 10 : 1.

5. Which of the following methods may be used for detection of microbial pathogens?

- A. Transcriptional profiling
- B. Metabolomics
- C. Sequencing
- D. DNA methylation
- E. Proteomics

Answer: C At this time, sequencing is used to detect and identify a microbial pathogen.

Ch / 44 REGENERATIVE MEDICINE, CELL, AND GENE THERAPIES

1. Meniscus repair by constructing an implantable scaffold seeded with mesenchymal stem cells that differentiate into chondrocytes would be an example of which of the following?

- A. Ex vivo gene therapy
- B. Autologous tissue meniscus implantation
- C. Tissue engineering
- D. Direct stem cell reprogramming
- E. Somatic gene therapy

Answer: C Rather than simply introducing cells into a diseased area, in tissue engineering, cells are embedded or seeded onto three-dimensional scaffolds (derived from different biomaterials) before transplantation. This can involve either (i) cellular scaffolds that are seeded ex vivo with cells before their in vivo transplantation, or (ii) acellular scaffolds that require the recipient's cells to repopulate the scaffold to reconstitute it after transplantation. To date, these efforts have mainly concentrated on the musculoskeletal system, as in the example presented. Ex vivo and somatic gene therapies by definition involve the transfer of specific genetic material into cells to correct or restore a cellular defect. Direct stem cell programming is the direct conversion of the phenotype of one cell type (e.g., fibroblasts) to another (e.g., chondrocytes). Autologous tissue meniscus implantation does not involve any type of cell and gene therapy. (See Tissue Engineering.)

2. To date, the only established clinical application of fetal-derived cell therapy has been in patients with which of the following?

- A. Parkinson disease
- B. Myocardial infarction
- C. Heart failure
- D. Blood product transfusion
- E. Cartilage repair

Answer: A Cells of fetal origin show enhanced proliferative capacity and enhanced ability to differentiate into mature or specialized cells. Although this form of cell therapy represents a form of regenerative medicine with great potential, the only fetal-derived cells that have been used in clinical applications to date are the dopaminergic cells derived from the developing fetal nervous system for the treatment of Parkinson disease. (See Engraftment of Fetal Tissue.)

3. Which one of the following is *not* a form of gene therapy?

- A. Transfection
- B. Transduction
- C. RNA interference
- D. Gene editing
- E. DNA electroporation

Answer: E Electroporation is a strictly *in vitro* research method in cell biology that electropermeabilizes cell membranes by an externally applied electrical field to introduce a piece of DNA (or other agents) into a cell. All the other choices are methods of gene therapy. Transfection is the direct delivery of naked DNA by injection, the use of liposomes, nanoparticles, and other means. Transduction is gene therapy that is mediated by viral vectors. RNA interference is a highly precise mechanism of regulating gene expression by sequence-directed silencing (by degrading specific messenger RNAs or by blocking their translation into protein). Gene editing is a way of correcting a pathogenic mutation in its natural gene location (rather than the more conventional gene therapy method of gene restoration, in which a whole gene is inserted into the genome). (See Gene Therapy Delivery Methods and Other Forms of Molecular Therapies: RNA Interference and Gene Editing under the main heading of Gene Therapy.)

Ch / 45 THE INNATE IMMUNE SYSTEM

1. Which of the following cell types is *not* considered to be a component of the innate immune system?

- A. Macrophages
- B. Neutrophils
- C. T lymphocytes
- D. Plasmacytoid dendritic cells
- E. Eosinophils

Answer: C T lymphocytes are important components of the adaptive immune system. T and B lymphocytes use mechanisms that rearrange DNA to form novel specific antigen-binding receptors. Cells of the innate immune system express pattern recognition receptors but do not express specific antigen-binding receptors.

2. Endosomal toll-like receptors (TLRs) recognize which of the following pathogen-associated molecular patterns (PAMPs)?

- A. Flagellin
- B. Lipopolysaccharide
- C. Antigenic peptides
- D. Nucleic acids

Answer: D TLRs are important innate immune system receptors that recognize patterns expressed by pathogenic microbes and some endogenous molecules. Cell surface-expressed TLRs recognize molecules that are typically expressed on the surface of microbes. Intracellular endosomal TLRs, such as TLR-3, -7, -8, and -9, recognize RNA or DNA. The sequestering of those nucleic acid-responsive TLRs protects the immune system from inadvertent activation by self-nucleic acids. However, in diseases such as systemic lupus erythematosus, nucleic acid-containing immune complexes can gain access to the endosomal TLRs and induce an innate immune response.

3. Which of the following innate immune system stimuli utilizes the inflammasome to trigger an inflammatory disease?

- A. Peptide-major histocompatibility class (MHC) class II complex
- B. Monosodium urate crystals
- C. Interleukin-6 (IL-6)
- D. Immunoglobulin E
- E. Complement

Answer: B Urate crystals access the components of the NOD-like receptors of the inflammasome, activate caspase 1, and induce the formation of IL-1, a pro-inflammatory mediator that can amplify an innate immune response. In some patients, this response leads to the acute inflammatory arthritis known as gout. Peptide-MHC class II complexes are stimuli for activation of an adaptive immune response. IL-6 is a broadly active cytokine, and immunoglobulin E is a component of an allergic response.

4. M2 macrophages participate in which of the following?

- A. Wound healing responses
- B. Antigen presentation
- C. Production of IL-12
- D. Recognition of oxidized low-density lipoprotein (LDL)
- E. Complement activation

Answer: A Although the designation of M1 and M2 macrophages is overly simplistic, macrophages do shift their functional program as the course of an immune response progresses toward a more chronic state, with M2 macrophages expanding and producing mediators, such as transforming growth factor- β and IL-10, that contribute to resolution of responses and repair of damaged tissue. Antigen presentation, production of IL-12, and recognition of oxidized LDL are more likely to be features of M1 macrophages.

5. Cells of the innate immune system produce soluble mediators that contribute to activation and expansion of an adaptive immune response. Among those mediators are which of the following?

- A. BAFF
- B. IL-23
- C. LL37
- D. All of the above
- E. A and B

Answer: E Macrophages and dendritic cells produce mediators that influence both the T and B cell arms of the adaptive immune response. IL-23 can promote generation of T-cell effector programs. BAFF is a B-cell survival and differentiation factor. LL37 is a cathelicidin that is produced by neutrophils and participates in the killing of phagocytosed microbes.

Ch / 46 THE ADAPTIVE IMMUNE SYSTEM

1. IgG antibodies are characterized by all of the following *except* which one?

- A. Two heavy chains and two light chains
- B. A common γ chain
- C. Disulfide bonds
- D. Subclasses

Answer: B IgG molecules consist of two identical heavy and two identical light chains, linked by disulfide bonds. IgG and IgA molecules include distinct subclasses encoded by distinct genomic DNA sequences. A common γ chain is a signaling component of certain cytokine and Fc receptors but is not a component of IgG antibodies.

2. CD4+ T cells recognize antigenic peptides presented on which of the following?

- A. Epithelial cells
- B. Major histocompatibility complex (MHC) class I molecules
- C. MHC class II molecules
- D. Costimulatory molecules
- E. CD80

Answer: C Antigenic peptides processed by specialized antigen-presenting cells associate with the peptide-binding cleft of MHC class II molecules and are recognized by the T-cell receptor expressed on CD4+ T cells. CD8+ T cells recognized antigenic peptides associated with MHC class I molecules. CD80 is an example of a costimulatory molecule expressed on antigen-presenting cells that supports the activation of T cells that have interacted with peptide- MHC complexes. Epithelial cells do not typically activate CD4+ T cells.

3. Which of the following functions is *not* provided by differentiated T cells?

- A. Production of interleukin-17 (IL-17)
- B. Lysis of virus-infected target cells
- C. Help for B-cell activation and differentiation
- D. Production of BAFF
- E. Production of interferon- γ

Answer: D The cytokine milieu of T cells contributes to differentiation of those cells to provide various effector functions. These include support for B-cell activation and differentiation (through CD154-CD40 interactions and production of IL-21), secretion of cytokines (interferon- γ) that support macrophage activation and delayed-type hypersensitivity reactions, induction of inflammatory responses (IL-17), and mediating the killing of virus-infected cells. Myeloid cells, rather than T cells, are the major producers of BAFF.

4. B cells minimize self-reactivity through a process called which of the following?

- A. Isotype switching
- B. Costimulation
- C. Somatic hypermutation
- D. Recombination
- E. Receptor editing

Answer: E Isotype switching, somatic hypermutation, and recombination are processes that promote the diversity of the B-cell repertoire. Costimulation of T-cell activation supports amplification of an adaptive immune response. Receptor editing modifies the sequence of the B-cell receptor to avoid production of autoreactive B cells.

5. Immunologic tolerance is mediated by all of the following *except* which of the following?

- A. Thymic deletion of T cells that recognize antigen with high affinity
- B. Regulatory T cells
- C. Toll-like receptor activation
- D. T-cell activation in the absence of costimulation
- E. It is mediated by all of the above.

Answer: C Central and peripheral tolerance mechanisms include thymic deletion of self-reactive T cells, T-cell activation without costimulation, and control of self-reactive cells by regulatory T cells. Toll-like receptor activation is an important feature of innate immune system activation.

Ch / 47 MECHANISMS OF IMMUNE-MEDIATED TISSUE INJURY

1. Type III hypersensitivity reactions are caused by tissue deposition of immune complexes which activate local effectors and lead to injury. Which of the following mediators are NOT characteristic of this pathway of inflammation?

- A. Fc receptors for IgE
- B. Complement
- C. Neutrophils
- D. Mononuclear phagocytes

Answer: A Type III responses are mediated by IgG directed against soluble antigens. Localized deposition of immune complexes activates mast cells, monocytes, neutrophils, and platelets bearing the Fc receptor for IgG (FcγR) and initiates the complement cascade, all effectors of tissue damage. Generation of complement components C3a and C5a recruits and stimulates inflammatory cells and amplifies effector functions. IgE does not participate in the inflammatory response. Of note, mast cells may be activated in type III responses through receptors for IgG or complement.

2. Type IV hypersensitivity reactions, as exemplified by the tuberculin test, does NOT require which of the following elements?

- A. IgG
- B. Macrophages
- C. TH1 effector cells
- D. IFN-γ

Answer: A The prototypic type IV hypersensitivity reaction is the tuberculin test, in which antigen is taken up, processed, and presented by macrophages. Type 1 helper T (TH1) effector cells that recognize the specific antigen are stimulated to release chemokines, which recruit macrophages to the site, and release cytokines including IFN-γ, which activate macrophages and enhance their release of inflammatory mediators. IgG does not participate in type IV hypersensitivity reactions.

3. In which of the following clinical situations are autoantibodies NOT critical triggers of tissue damage?

- A. Asthma
- B. Pemphigus vulgaris
- C. Graves disease
- D. Systemic lupus erythematosus

Answer: A IgE antibodies against innocuous environmental antigens initiate asthma, not autoantibodies. Autoantibodies against TSH receptors act as agonists in Graves disease. Autoantibodies against desmoglein-3 effect adhesion between epidermal keratinocytes and cause blister formation. In systemic lupus erythematosus, inflammation is initiated by deposition of immune complexes containing autoantibodies directed against common cellular constituents (e.g., DNA and ribonucleolar proteins).

4. A syndrome similar to serum sickness occurs in which of the following infections?

- A. Hepatitis B
- B. Tuberculosis
- C. Pneumococcal pneumonia
- D. Influenza

Answer: A A syndrome similar to serum sickness occurs in chronic infections in which pathogens persist in the face of continued immune response. Hepatitis B virus infection may be associated with immune complex deposition early in its course, during a period of antigen excess, because antibody production in response to hepatitis B surface antigen is as yet relatively insufficient. Efficiency of clearance of immune complexes depends on their size and valence. Smaller immune complexes, which form in antigen excess—as occurs early in an immune response—circulate in the blood and are deposited in blood vessels, where they initiate inflammatory reactions and tissue damage through interactions with FcγRs and complement receptors. In influenza and pneumococcal pneumonia, there is no clinical evidence of systemic immune complex deposition. Tuberculosis generates T-cell responses.

5. The effector mechanisms that lead to tissue damage in autoimmune diseases are similar to those elicited in response to environmental antigens that result in allergy. Which hypersensitivity reaction is correctly matched to an autoimmune condition that occurs through a similar mechanism?

- A. Systemic lupus erythematosus and serum sickness
- B. Idiopathic thrombocytopenia purpura and asthma
- C. Multiple sclerosis and heparin-induced thrombocytopenia
- D. Myasthenia gravis and atopic dermatitis

Answer: A Systemic lupus erythematosus, the prototypical immune complex–mediated autoimmune disease, is characterized by circulating IgG directed against common cellular constituents, typically DNA and DNA-binding proteins. Like in the case of serum sickness, small immune complexes are deposited in skin, joints, and glomeruli and initiate local tissue damage. Idiopathic thrombocytopenia purpura, like type II hypersensitivity reactions, is mediated by autoantibodies that are directed to platelet surface antigens, whereas asthma is triggered by IgE against innocuous environmental antigens (type I hypersensitivity reaction). T cells are key effectors in multiple sclerosis, whereas heparin-induced thrombocytopenia is caused by IgG autoantibodies. Myasthenia gravis is caused by IgG autoantibodies that recognize acetylcholine receptors and impair neuromuscular signaling, whereas atopic dermatitis is mediated by T cells.

1. What statement is false about the alternate pathway of complement activation?

- A. It serves as a feedback or amplification loop for each pathway.
- B. It mediates lysis and cell damage in several types of hemolytic disorders.
- C. It is involved in debris removal and wound repair.
- D. It requires lectins and antibodies to be initiated.

Answer: D The alternate pathway is the original complement system. For example, it is present in insects and echinoderms and functions in hemolymph similar to its role in blood vertebrates. It is often called the “guardian of the intravascular space,” being particularly designed to prevent invasion by bacteria. It is continuously “turning over” at a low rate. Antibody and lectins are more evolutionary recent means to specifically target complement activation.

2. Which statement is *not* true of the classical pathway?

- A. In conjunction with IgG and IgM, the classical pathway mediates tissue damage in autoimmune diseases.
- B. A complete deficiency of an early component predisposes to SLE.
- C. A total complement titer (CH50 or THC) measures the quantity of hemolytic activity in this pathway.
- D. Proteins such as CRP and serum amyloid protein (SAP) also can activate the classical pathway.
- E. All are true.

Answer: E It requires only a single IgM or two IgGs in close proximity to activate the classical complement pathway. IgA and IgE do not activate the classical complement pathway.

3. A deficiency of a complement inhibitor at the steps of C3 and C5 activation leads to all of the following except:

- A. excessive production of the C3a and C5a anaphylatoxins.
- B. excessive production of opsonins and the membrane attack complex.
- C. systemic lupus erythematosus and closely related rheumatic diseases.
- D. renal disease (atypical hemolytic uremic syndrome, membranoproliferative glomerulonephritis, C3 glomerulonephritis, and C3 glomerulopathies).

Answer: C Excessive activation at sites of injury or degeneration is a hallmark of inadequately regulated C3 and C5 convertases. The diseases for which this type of pathogenesis has been most studied are atypical hemolytic uremic syndrome and age-related macular degeneration. The other commonly observed phenotype is renal disease as described in Answer D.

4. Which statement is *not* true?

- A. CP is activated by the Fc portion of IgG or IgM engaging C1q, which is part of C1 complex.
- B. Complement receptor one (CR1, CD35) on RBCs serves as a taxi or ferry to take C4b and C3b bearing immune complexes to liver and spleen for disposal.
- C. Only a limited number of specific foreign antigens can be coated with complement fragments.
- D. Complement proteins in blood are synthesized by the liver, but most cell types also express complement proteins locally.

Answer: C Almost all foreign materials become coated with complement C3 fragments. Of note, a role in host defense and response to injury for local synthesis of complement components remains to be definitely established.

5. The C3a and C5a anaphylatoxins accomplish all but which one of the following?

- A. Engage their specific receptors to activate many cell types.
- B. If liberated in substantial amounts, they can lead to shock and death.
- C. They are responsible for opsonic activity of the complement system.
- D. Both are produced by all complement pathways.

Answer: C C3a and C5a are liberated in substantial amounts and this occurs in seconds. It is an early warning system to the host cell to develop a proinflammatory environment. The major opsonin of the complement system is C3b and its subsequent limited proteolytic degradation fragments. C4b is also an opsonin if the classical pathway or lectin pathway is activated.

Ch / 53 CARDIAC FUNCTION AND CIRCULATORY CONTROL

1. What types of muscle are found in the heart?

- A. Skeletal and cardiac
- B. Cardiac and smooth
- C. Only smooth
- D. Only cardiac
- E. Smooth, cardiac, and skeletal

Answer: B Cardiac muscle is termed striated muscle, and it is anatomically and mechanistically similar to but distinct from skeletal muscle. Cardiac muscle accounts for the contractile function of the heart. Smooth muscle composes the media of the arteries in the heart and is responsible for arterial contraction and tone. There is no skeletal muscle in the heart.

2. Which of the following functions is *not* a property of adult mammalian cardiac muscle?

- A. Rhythmic contractions to determine cardiac output
- B. Relaxation to allow a cardiac chamber to refill
- C. Hypertrophy in response to increased afterload (e.g., hypertension)
- D. Rate-dependent increase in contractility
- E. Regeneration after injury

Answer: E Adult cardiomyocytes are terminally differentiated, which means that they no longer can divide to form additional cells. They respond to stress by undergoing hypertrophy, a process in which individual cells enlarge, but the number of cells remains constant.

3. Which of the following is *not* true?

- A. Troponin C is a critical protein in cardiac muscle.
- B. Potassium is the ion that activates skeletal and cardiac muscle contraction.
- C. The mechanism of cardiac muscle contraction involves shortening of the sarcomeres.
- D. Thick and thin filaments are present in cardiac, skeletal, and smooth muscle sarcomeres.
- E. Both pharmacomechanical and electromechanical processes can activate cardiac muscle.

Answer: B Potassium channels are involved in repolarization of the cardiac action potential, but calcium is the ion that activates muscle contraction by binding to troponin C and allowing actin-myosin cross-bridging to occur, thereby shortening the sarcomere. The source of calcium is intracellular calcium release from the sarcoplasmic reticulum through the ryanodine receptor/calcium release channel.

4. Phase 0 of the action potential, when the cardiac muscle cell is depolarized, represents influx of which of the following ions?

- A. Calcium
- B. Copper
- C. Potassium
- D. Magnesium
- E. Sodium

Answer: E Opening of the sodium channel, which is the initial event in the action potential, allows sodium to rush into the cardiomyocyte and to depolarize the membrane potential. Depolarization of the cell membrane opens voltage-gated calcium channels; repolarization occurs when potassium channels are activated.

5. Which of the following steps in cardiac muscle excitation-contraction coupling does *not* require ATP consumption?

- A. Pumping calcium back into the sarcoplasmic reticulum
- B. Calcium release from the sarcoplasmic reticulum
- C. Actin-myosin cross-bridge formation and contraction
- D. Sodium-potassium exchange across the plasma membrane
- E. Extrusion of calcium from the cell across the plasma membrane

Answer: B The release of calcium from the sarcoplasmic reticulum through the ryanodine receptor/calcium release channel occurs when the channel opens, allowing calcium to flow out of the sarcoplasmic reticulum and down its concentration gradient (millimolar inside the sarcoplasmic reticulum and nanomolar in the cytoplasm). Thus, no energy is required.

Ch / 55 ECHOCARDIOGRAPHY

1. Echocardiographic three-dimensional left ventricular volumes measured in a 55-year-old man receiving cardiotoxic chemotherapy are 120 mL at end diastole and 60 mL at end systole. Left ventricular ejection fraction is

- A. 30%
- B. 40%
- C. 50%
- D. 60%
- E. 70%

Answer: C Left ventricular ejection fraction (EF) is calculated as stroke volume (end-diastolic volume [EDV] minus end-systolic volume [ESV]) divided by end-diastolic volume multiplied by 100%. In this case:

$$EF = (EDV - ESV) / EDV \times 100\% = (120 - 60) / 120 \times 100\% = 50\%$$

2. Echocardiographic evaluation in an 82-year-old woman with a systolic murmur shows a heavily calcified aortic valve. The severity of valve obstruction is best evaluated by

- A. Three-dimensional imaging
- B. Pulsed Doppler
- C. Tissue Doppler
- D. Color flow Doppler imaging
- E. Continuous-wave Doppler

Answer: E Valve obstruction with reduced systolic opening of the aortic valve results in an increased velocity across the valve. Velocity is a direct measure of the severity of the stenosis and predicts clinical outcome. The velocity (v) across a stenotic valve is related to the pressure gradient (ΔP) as stated in the Bernoulli equation, $\Delta P = 4v^2$. Measurement of high velocities requires continuous-wave Doppler ultrasound, which typically is not available on point-of-care ultrasound systems. Three-dimensional imaging allows more accurate identification of the number of valve leaflets and may show the degree of valve opening, but it is not accurate for measuring the severity of stenosis. Pulsed Doppler velocity measurements are accurate only at low velocities. Tissue Doppler measures the velocity of myocardial motion, which reflects left ventricular systolic and diastolic function, not the severity of stenosis. Color Doppler flow imaging is useful for visualizing the location of intracardiac flow disturbances but cannot measure high-flow velocities.

3. A 68-year-old man presents with a 2-week history of increasing dyspnea and is found to be in atrial fibrillation with a ventricular rate of 120 beats per minute. The most appropriate test to evaluate for left atrial thrombus before cardioversion is

- A. Point-of-care echocardiography
- B. Transthoracic echocardiography
- C. Intracardiac echocardiography
- D. Transesophageal echocardiography
- E. No testing is needed.

Answer: D In patients being considered for cardioversion for atrial fibrillation, clinical approaches to avoiding systemic embolization with restoration of normal sinus rhythm include effective anticoagulation for several weeks before cardioversion or exclusion of a left atrial thrombus by visualizing the left atrial appendage. Left atrial thrombi cannot be accurately diagnosed by transthoracic or point-of-care echocardiography because atrial thrombi occur most often in the atrial appendage, which is distant from the transducer and difficult to visualize. Transesophageal echocardiography provides superior images of the left atrial appendage and is reliable for exclusion of atrial thrombus when images are obtained in at least two orthogonal views with use of zoom mode and a high-frequency transducer. Intracardiac echocardiography also may provide images of the left atrial appendage and may be used during an electrophysiologic or interventional cardiology procedure. However, intracardiac echocardiography is not used as a stand-alone diagnostic test.

4. A 63-year-old woman presents with a 6-month history of midsternal chest pressure that occurs both at rest and with exertion. Her only cardiac risk factor is chronic hypertension with medical therapy. She also has osteoarthritis of her knees and is able to walk only short distances. The baseline electrocardiogram shows left ventricular hypertrophy with a strain pattern. An appropriate diagnostic test to evaluate this patient for coronary disease is

- A. Treadmill electrocardiographic stress test
- B. Treadmill echocardiographic stress test
- C. Supine bicycle nuclear perfusion stress test
- D. Dobutamine stress echocardiography
- E. Coronary angiography

Answer: D Coronary artery disease may explain symptoms in this patient, so stress testing is appropriate for diagnosis and risk stratification. Electrocardiographic stress testing will not be diagnostic because her abnormal baseline electrocardiogram limits the accuracy of changes in ST segments with exercise for diagnosis of coronary disease. This patient also has significant lower extremity arthritis, which limits her ability to exercise. Diagnostic accuracy with an exercise test (either treadmill or bicycle) requires that the patient reach 85% of the maximum predicted heart rate for age. Exercise testing is likely to be nondiagnostic in this patient with lower extremity arthritis. Pharmacologic stress testing, either dobutamine stress echocardiography or pharmacologic nuclear perfusion imaging, is the most appropriate test choice. Coronary angiography would be appropriate only if stress testing suggests high-risk coronary disease that might benefit from revascularization.

5. A 68-year-old man presents to the emergency department with a 1-hour history of severe chest pain and diaphoresis. The electrocardiogram shows ST depression in the lateral leads. Point-of-care echocardiography is appropriate to evaluate for

- A. Aortic dissection
- B. Aortic valve stenosis
- C. Acute anterior infarction
- D. Mitral valve vegetation
- E. Pericardial effusion

Answer: E All of these diseases can be accurately diagnosed by a complete transthoracic or transesophageal echocardiographic study under the supervision of a cardiologist. Point-of-care ultrasound systems typically have fewer features and limited image quality compared with complete diagnostic ultrasound systems. In addition, point-of-care ultrasound is performed and interpreted by physicians with limited training in this modality. The recommended scope of practice for point-of-care ultrasound studies includes diagnosis of pericardial effusion. In contrast, diagnosis of aortic dissection requires transesophageal echocardiographic or computed tomographic or magnetic resonance imaging. Diagnosis of aortic valve stenosis requires continuous-wave Doppler recording of the transvalvular velocity by an experienced sonographer. Acute anterior myocardial infarction results in hypokinesis or akinesis of the anterior wall, which can be visualized by echocardiography. Point-of-care ultrasound allows evaluation of global left ventricular systolic function, but evaluation of regional myocardial dysfunction is more challenging and requires additional training and experience. A mitral valve vegetation might be diagnosed on transthoracic imaging, but transesophageal imaging often is required. Mitral valve vegetations are likely to be missed with current point-of-care ultrasound systems or by less experienced clinicians.

Ch / 56 NONINVASIVE CARDIAC IMAGING

1. Which statement regarding the evaluation of the heart on chest radiography is correct?
- A. The main value of a chest radiograph is the ability to diagnose congenital cardiac disorders owing to a large number of disease-specific imaging signs.
 - B. Since the advent of echocardiography, the chest radiograph no longer plays a role in the evaluation of the patient with cardiac disease.
 - C. The chest radiograph is useful to monitor the progression of cardiac disease and its response to treatment.
 - D. The chest radiograph is an accurate imaging modality to assess the exact position of an implanted device.
 - E. All of the above

Answer: C Although echocardiography and the other cross-sectional imaging modalities have replaced chest radiography for the diagnosis of most cardiac diseases, the value of chest radiography is its ability to monitor the progression of cardiac disease and its response to treatment rapidly and inexpensively. The diagnosis of congenital cardiac disorders is made with echocardiography, cardiac catheterization, and cardiac magnetic resonance imaging and computed tomography. Despite the ready availability of echocardiography, the chest radiograph is valuable for rapid evaluation of changes in heart size and pulmonary vascularity, as well as signs of heart failure. The radiograph shows the position of a device on a two-dimensional image, but assessment of the exact position may require cross-sectional imaging.

2. Which of the following groups of patients are good candidates for coronary artery calcium scoring?
- A. after coronary artery bypass surgery
 - B. after coronary stenting
 - C. High risk Framingham score
 - D. Intermediate risk Framingham score
 - E. Low risk Framingham score

Answer: D In patients at intermediate risk, knowing the coronary artery calcium score might change management in terms of aggressive lipid lowering. High-risk patients should already be receiving aggressive therapy, and no additional therapy is needed in low-risk patients.

3. Coronary computed tomographic angiography (CTA) is useful for the following indication:
- A. Evaluating native vessels in post-CABG patients
 - B. Evaluating in-stent restenosis
 - C. Screening asymptomatic patients with strong family histories of CHD
 - D. Evaluating low-to-intermediate risk patients in the emergency department
 - E. All of the above

Answer: D Recent randomized trials have demonstrated the utility of CTA compared with standard evaluation in the emergency department. Native vessels are difficult to image post-CABG because they tend to shrink and calcify. Imaging within stents remains a challenge. Coronary CTA is not appropriate as a screening test in asymptomatic individuals.

4. A 62-year-old white male presents with substernal chest discomfort that is “aching” in nature and occurs with mild exertion but also occasionally at rest. It seems to radiate to the throat and is relieved in a few minutes with rest. He has also noted some recent shortness of breath when walking up hills. He has a history of gastroesophageal reflux disease and a hiatal hernia. He has no history of hypertension, diabetes, or smoking. His BMI is 35, and his LDL cholesterol is 162 mg/dL. His father died suddenly of an unknown cause when he was 60 years old. He has been on a Mediterranean diet for the past 2 months. On physical examination, his blood pressure is 130/80 and the remainder of his

exam is unremarkable. The patient is referred by his physician for an exercise SPECT myocardial perfusion scan. He exercises to a workload of 6 METS and a peak heart rate representing 77% of his age-predicted maximum. He stopped because of dyspnea and some slight chest discomfort. His exercise ECG showed some ST segment flattening, but not depressed more than 0.5 mm. These changes resolved in recovery. His myocardial perfusion scan showed no perfusion defects. The left ventricular cavity size appeared larger on the stress than on the rest images. There was diffuse hypokinesis, and the left ventricular ejection fraction was 42%. Which one of the following statements is INCORRECT regarding this patient?

- A. His blood pressure does not need to be reduced further
- B. He most likely has a nonischemic cardiomyopathy
- C. He most likely has multivessel coronary artery disease
- D. His diet has been shown to reduce the risk for developing coronary artery disease
- E. According to guidelines, he should be started on statin therapy

Answer: B He does not have a nonischemic cardiomyopathy. His SPECT scan shows transient ischemic cavity dilation of the left ventricle in association with diffuse left ventricular hypokinesis. The reason he has no perfusion defects is because of balanced ischemia in the supply regions of all 3 major coronary vessels. No focal defects will be observed if the reduction in perfusion is rather homogeneous in the myocardium. He has an intermediate-high pretest likelihood of coronary disease by clinical criteria. His blood pressure is adequately controlled. Diets such as the Mediterranean diet have been shown to reduce the risk of coronary disease. Due to the high likelihood of coronary disease, he should be started on statin therapy and is a good candidate for coronary arteriography because of likely multivessel disease with a reduced ejection fraction.

1. Which of the following patients is suitable for cardiac catheterization?

- A. A 60-year-man with atypical chest discomfort, no risk factors for coronary artery disease, a negative stress test result, and relief of symptoms with famotidine
- B. A 67-year-man with prior coronary artery bypass surgery who is asymptomatic and fully active and now wants to buy new life insurance
- C. A 39-year-old woman with shortness of breath and a midsystolic click on physical examination
- D. A 41-year-old man with palpitations
- E. A 53-year-old man with palpitations, hypertension with β -blockers and aspirin, and reversible defect on stress perfusion imaging

Answer: E Indications for cardiac catheterization and coronary angiography according to guidelines recommend invasive angiography for patients with objective evidence of myocardial ischemia after treatment with medical therapy. Patient A has no ischemia and likely has gastrointestinal symptoms. Patient B is asymptomatic and is not in need of angiography. Patient C needs an echocardiogram before consideration of invasive assessment. Patient D has palpitations of unknown cause and could be evaluated with an echocardiogram, ambulatory arrhythmia monitoring, or a stress test, but cardiac catheterization is not indicated unless an ischemic origin is demonstrated for his palpitations.

2. Which patient has the highest risk of complications of cardiac catheterization?

- A. An 82-year-old woman with hypertension
- B. A 76-year-old man with creatinine concentration of 1.7 mg/dL
- C. A 61-year-old woman with body mass index of 28
- D. A 58-year-old man with a heart murmur
- E. A 40-year-old woman with a history of syncope

Answer: B Cardiac catheterization requires administration of radiocontrast media, which can impair renal function. In patients with preexisting renal failure, worsening renal failure is likely. Measures to prevent contrast-induced renal failure include preprocedural hydration to increase urine output.

3. Which of the following conditions does not require a right-sided heart hemodynamic study?

- A. Left ventricular systolic failure
- B. Left ventricular diastolic failure
- C. Pericardial disease
- D. Aortic stenosis
- E. Severe three-vessel coronary artery disease

Answer: E Right-sided heart catheterization is not routine for coronary artery disease but is mandatory for valvular heart disease and routine for heart failure, right ventricular dysfunction, pericardial disease, cardiomyopathy, intracardiac shunts, and congenital abnormalities.

4. Which of the following is an absolute contraindication to cardiac catheterization?

- A. Ventricular tachycardia
- B. Sepsis
- C. Inadequate imaging equipment
- D. Uncontrolled hypertension
- E. Creatinine concentration of 2.4 mg/dL

Answer: C Absolute contraindications to catheterization include inadequate facilities and patient refusal. Relative contraindications include severe uncontrolled hypertension, ventricular arrhythmias, recent acute stroke, severe anemia, active gastrointestinal bleeding, allergy to radiographic contrast material, acute renal failure, uncompensated heart failure such that the patient cannot lie flat, unexplained febrile illness or untreated active infection, electrolyte abnormalities (e.g., hypokalemia), severe coagulopathy, pregnancy, uncontrolled arrhythmias or hypertension, and an uncooperative patient.

5. Which of the following coronary anomalies is associated with sudden death?

- A. A right coronary artery originating from the left coronary sinus
- B. A right coronary artery originating from the anterior coronary cusp
- C. A left coronary artery that originates from the right coronary cusp and traverses between the aorta and pulmonary artery
- D. A circumflex coronary artery that arises from the right coronary cusp and traverses between the aorta and pulmonary artery
- E. A circumflex coronary artery that arises from the right coronary cusp and traverses behind the aorta

Answer: C The most critical coronary anomaly is when the left main coronary artery arises from the right cusp and traverses a course between the aorta and pulmonary artery. The artery's initial course through the aortic wall creates a narrow oval opening; when the aorta stretches during exercise, coronary blood flow is limited.

1. Which of the following statements is true regarding heart failure epidemiology?
- A. White patients have an increased incidence of heart failure compared with black patients.
 - B. Black patients are at an increased risk for rehospitalization for heart failure.
 - C. Women have better long-term survival after the diagnosis of heart failure compared with men.
 - D. The heart failure with preserved ejection fraction population represents approximately a third of overall heart failure cases.
 - E. The absolute mortality rate after the diagnosis of heart failure is approximately 25% at 5 years.

Answer: B Black patients are at an increased risk for development of heart failure and have an increased risk for heart failure rehospitalization compared with white patients. Median survival is lower in women than in men. Heart failure with preserved ejection fraction represents approximately half of heart failure cases. The absolute mortality rate after heart failure diagnosis is approximately 50% at 5 years.

2. Which is the correct statement regarding guideline recommendations for the diagnosis of heart failure?
- A. Routine repeated measurements of left ventricular function in the absence of a clinical status change are reasonable.
 - B. Measurement of natriuretic peptides is recommended to support the diagnosis of heart failure in ambulatory patients with dyspnea as well as in those with possible acute heart failure.
 - C. There is an established role for routine or periodic invasive hemodynamic measurements in the management of heart failure.
 - D. Endomyocardial biopsy should be performed in the routine evaluation of patients with heart failure, given the need to diagnose the underlying etiology.
 - E. On cardiopulmonary exercise testing, a peak oxygen uptake of more than 20 mL/kg/minute is associated with a relatively poor prognosis.

Answer: B Routine repeated measurements of left ventricular function in the absence of a clinical status change or treatment intervention should not be performed. An echocardiogram should be obtained during the initial evaluation of patients with heart failure to assess ventricular function and valve function. Measurement of natriuretic peptides is recommended to support the diagnosis of heart failure in ambulatory patients with dyspnea as well as in those with possible acute heart failure. Routine or periodic invasive hemodynamic measurements in the management of heart failure are not recommended. Guidelines indicate that endomyocardial biopsy should not be performed in the routine evaluation of patients with heart failure. However, endomyocardial biopsy may be useful in patients presenting with heart failure when a specific diagnosis is suspected that would influence therapy. A peak oxygen uptake of less than 14 mL/kg/minute is associated with a relatively poor prognosis.

3. Which of the following statements is correct regarding the history and physical examination in heart failure patients?
- A. Sleep-disordered breathing has a similar prevalence in heart failure patients and in the general population.
 - B. Lower extremity edema is a relatively specific sign of underlying heart failure.
 - C. Rales on the pulmonary examination are common in chronic heart failure patients because of elevated ventricular filling pressures.
 - D. An apical S3 gallop is a strong indicator of left ventricular systolic dysfunction and elevated left ventricular filling pressures.
 - E. The blood pressure is most commonly low (systolic blood pressure <90 mm Hg) in chronic heart failure patients.

Answer: D An apical S3 gallop is a strong indicator of left ventricular systolic dysfunction and elevated left ventricular filling pressures. Sleep-disordered breathing is prevalent in heart failure patients and is associated with increased morbidity and mortality. Upward of 70% of heart failure patients have sleep-disordered breathing. The majority of patients with heart failure have normal findings on pulmonary examination. Despite having an elevation in left ventricular filling pressures that is transmitted back into the left atrium and pulmonary vasculature, most patients with compensated heart failure do not have evidence of pulmonary congestion. In heart failure patients, the blood pressure is most commonly normal or high, but it may be low (systolic blood pressure <90 mm Hg) in advanced low-output heart failure. Orthopnea (not lower extremity edema) is a relatively specific sign of heart failure.

Ch / 60 DISEASES OF THE MYOCARDIUM AND ENDOCARDIUM

1. A 35-year-old man without vascular disease risk factors is found to have an abnormality on the electrocardiogram (ECG) with left axis deviation (−45 degrees) and a prolonged PR interval (260 msec) in association with mild left ventricular dilation and a mildly reduced ejection fraction (56%). Physical examination is unremarkable. A diagnosis of dilated cardiomyopathy with conduction disease is made. Which of the following is the most appropriate recommendation?

- A. Orchestrate a three-generation family history focusing on premature cardiac disease.
- B. Perform myocardial perfusion studies to determine the need for coronary angiography.
- C. Perform computed tomography or invasive coronary angiography to exclude significant coronary artery disease.
- D. Initiate and up-titrate treatment with a β -blocker and an angiotensin-converting enzyme inhibitor.
- E. Refer to a geneticist for mutation analysis.

Answer: A A clinical presentation with unexplained conduction disease and left ventricular dysfunction usually results in a diagnosis of dilated cardiomyopathy (in Europe) or nonischemic cardiomyopathy (in the United States). When conduction disease is part of the early presentation of a dilated or nonischemic cardiomyopathy, it is a “red flag” for an arrhythmic form of dilated cardiomyopathy. A family history focusing on relatives who required pacemakers, had ventricular arrhythmias, died suddenly, or had associated phenotypes (e.g., skeletal myopathy, retinitis pigmentosa, sensory neural deafness) may provide clues to the ultimate diagnosis, requirements for genetic testing, and potential need for an implantable cardioverter-defibrillator. (Rapezzi C, Arbustini E, Caforio AL, et al. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2013;34:1448-1458.)

2. An asymptomatic 70-year-old man is found to have an abnormality on the 12-lead ECG during a preoperative clinical evaluation. A two-dimensional echocardiogram reveals 2-cm asymmetrical septal hypertrophy without features of a left ventricular outflow tract gradient. Familial evaluation for hypertrophic cardiomyopathy reveals that his 43-year-old son has an abnormality on the ECG but normal findings on echocardiography, whereas an 18-year-old asymptomatic grandson has 2.2-cm asymmetric septal hypertrophy without left ventricular outflow tract obstruction. A 24-hour ECG reveals three beats of nonsustained ventricular tachycardia at 130 beats per minute. The estimated absolute 5-year risk for sudden cardiac death in the grandfather is 3.4%; in the son, 2.2%; and in the grandson, 5.2%. Which of the following recommendations is most appropriate?

- A. The grandson should receive an implantable cardioverter-defibrillator.
- B. Mutation analysis should be performed to enable genetic cascade screening of the family.

- C. Septal reduction therapies should be considered if the grandfather's exercise capacity is less than 75% of predicted during objective testing.
- D. Both the patient and his grandson should receive an implantable cardioverter-defibrillator.
- E. No interventions are warranted in the patient, his son, or his grandson, but serial evaluations should continue to assess risk of atrial fibrillation, emboli, and serious ventricular arrhythmia with a view to early introduction of prophylactic therapy.

Answer: A Nonsustained ventricular tachycardia recorded during ambulatory ECG monitoring is usually asymptomatic, brief, and at rates of 140 to 160 beats per minute. It is, however, associated with increased risk of sudden death, particularly in the young, in whom it carries a relative risk of approximately 5 and an absolute 5-year sudden cardiac death event rate of 5 to 6% in a 20-year-old compared with a relative risk of 2 or 3 and absolute 5-year risk of 4% in a 70-year-old. Ultimately, the decision to implant an implantable cardioverter-defibrillator is individualized on the basis of the physician's assessment of the level of risk and the level of risk acceptable to the patient. The estimated events risks quoted here are excessive in an adolescent but only mildly increased in someone in the seventh to eighth decade. (O'Mahony C, Lambiase PD, Quarta G, et al. The long-term survival and the risks and benefits of implantable cardioverter defibrillators in patients with hypertrophic cardiomyopathy. *Heart*. 2012;98:116-125. O'Mahony C, Tome-Esteban M, Lambiase PD, et al. A validation study of the 2003 American College of Cardiology/European Society of Cardiology and 2011 American College of Cardiology Foundation/American Heart Association risk stratification and treatment algorithms for sudden cardiac death in patients with hypertrophic cardiomyopathy. *Heart*. 2013;99:534-541. O'Mahony C, Jichi F, Pavlou M, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy [HCM Risk-SCD]. *Eur Heart J*. 2014;35:2010-2020.)

3. An 18-year-old African American female marathon runner presents with postexertional syncope. Her 12-lead ECG tracing is abnormal, with a biphasic T wave in leads V2 to V4. Family history reveals a maternal nephew who died suddenly at the age of 23 years while dancing in a discotheque. Her two-dimensional echocardiogram is unremarkable. Which of the following is incorrect?
- A. An implantable cardioverter-defibrillator should be recommended, given the family history and the postexertional syncopal episode.
 - B. An abnormality on the ECG is often the earliest manifestation of hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and cardiac sarcoidosis.
 - C. Imaging with two-dimensional echocardiography or cardiac magnetic resonance imaging provides the definitive diagnosis for hypertrophic cardiomyopathy.
 - D. Familial evaluation is paramount to determine a diagnosis and potential risk to the patient.
 - E. A biphasic T wave in V2 and V3 is a recognized normal variant in African American athletes.

Answer: A Electrocardiographic abnormalities in heart muscle disease are rarely diagnostic but are often the earliest manifestation of disease and warrant further diagnostic evaluation. Inverted or biphasic T waves in V1 to V3 are seen in African American athletes, but changes that extend to V4 or beyond are usually associated with myocardial disease. New-onset conduction disease and ventricular arrhythmia are common presenting features of Chagas disease and cardiac sarcoidosis, whereas conduction disease is rarely seen early in arrhythmogenic right ventricular cardiomyopathy or hypertrophic cardiomyopathy. Demonstration of left ventricular hypertrophy with echocardiographic or cardiac magnetic resonance imaging is usually diagnostic of hypertrophic cardiomyopathy, but concern should be raised about the accuracy of the measurements when the ECG recording is normal. Imaging abnormalities often provide the definitive diagnosis but are late manifestations of arrhythmogenic right ventricular cardiomyopathy because they reflect myocyte cell death with replacement scar. The onset of dilated cardiomyopathy in adults is usually insidious, with slow progression of left ventricular dilation and impaired contraction. The implantable cardioverter-defibrillator may be life-saving, but it is associated with lifelong consequences and should not be recommended without a diagnosis and clear estimate of sudden death risk. (Sheikh N, Papadakis M, Ghani S, et al. Comparison of electrocardiographic criteria for the detection of cardiac abnormalities in elite black and white athletes. *Circulation*. 2014;129:1637-1649.)

Ch / 62 APPROACH TO THE PATIENT WITH SUSPECTED ARRHYTHMIA

1. The most important factor in determining the prognosis in patients with suspected arrhythmias is which of the following?
- A. The existence of underlying structural heart disease (e.g., coronary artery disease, prior myocardial infarction, or ventricular dysfunction)
 - B. The duration of the symptoms
 - C. The frequency of the symptoms
 - D. Family history of palpitations
 - E. Responsiveness to Valsalva maneuvers

Answer: A See Clinical Manifestations. In general, the most important factor determining the prognosis of arrhythmias is whether they occur in the setting of underlying heart disease. Specifically, patients with heart failure, prior myocardial infarction, aortic stenosis, and hypertrophic cardiomyopathy have a much higher likelihood of having ventricular tachycardia or ventricular fibrillation that may lead to a cardiac arrest than do patients with a normal heart. In addition, other nonlethal arrhythmias, such as atrial fibrillation, also are more prevalent in these patients. Evaluation and treatment of symptoms of a suspected arrhythmia are therefore different in patients with and without structural heart disease.

2. A 25-year-old patient without any known prior cardiac disease presents with a 3-month history of intermittent palpitations, which occur every few weeks, persist for up to about 5 minutes, and spontaneously resolve. On occasion they are accompanied by dizziness, and on a recent episode he had a syncopal episode. What would be the most appropriate *first* test to obtain for him in the evaluation of his symptoms?
- A. A cardiac catheterization
 - B. A head-up tilt table test
 - C. A 12-lead electrocardiogram (ECG)
 - D. A 24-hour Holter monitor
 - E. A complete blood count and electrolyte panel

Answer: C See Diagnostic Tests: Electrocardiography. Even though the patient is not having palpitations at this time, there may be clues on the ECG to indicate their cause and to guide further evaluation. For example, ventricular preexcitation makes supraventricular tachycardia (SVT) and Wolff- Parkinson-White syndrome the likely diagnosis. In addition, other syndromes such as the long QT syndrome, hypertrophic cardiomyopathy, or other abnormalities may be seen on a baseline ECG. The evaluation would not end with an ECG and would likely require further ambulatory monitoring. However, because the symptoms do not occur every day, a 24-hour Holter monitor is unlikely to capture the rhythm during his symptoms.

3. What type of ambulatory monitoring would be most appropriate for a patient who has intermittent palpitations that occur every 1 to 2 weeks?
- A. A 48-hour Holter monitor
 - B. An implantable loop recorder
 - C. Ambulatory blood pressure monitor
 - D. A wearable event monitor
 - E. A wearable defibrillator vest

Answer: D See Diagnostic Tests: Ambulatory Monitoring. Because the symptoms occur less frequently than daily, it is very unlikely that a 24- or 48-hour Holter monitor will detect an event. A wearable event monitor, which can be worn for 3 to 4 weeks, is likely to capture an event. Although an implantable loop recorder would likely capture an event, it is inappropriate in this setting because of its expense and invasive nature. An ambulatory blood pressure monitor is unable to detect an arrhythmia. A wearable defibrillator vest is not necessary because the patient has not had a cardiac

arrest. Assuming a baseline ECG was obtained as part of the initial evaluation (see previous question), an ECG following an episode when the patient is asymptomatic is unlikely to be helpful.

4. When a patient presents in a narrow complex tachycardia, which of the following is the *most* useful diagnostic test?

- A. Carotid sinus massage
- B. A 12-lead ECG of the tachycardia
- C. Administration of adenosine while recording a continuous 12-lead ECG
- D. An echocardiogram while still in the tachycardia
- E. A nuclear stress test

Answer: C See Diagnostic Tests. Adenosine is useful for narrow complex tachycardias both diagnostically and therapeutically. For example, if the tachycardia continues with flutter waves or P waves during atrioventricular (AV) block, then a diagnosis of atrial flutter or atrial tachycardia is established. Likewise, the termination of the tachycardia with a P wave that is not conducted to the ventricle is much more likely to be an AV or AV nodal re-entrant tachycardia. In addition, adenosine after termination of the tachycardia can bring out ventricular preexcitation suggestive of Wolff-Parkinson-White syndrome that may be otherwise subtle on the baseline ECG. Comparison of the narrow complex tachycardia to the baseline ECG can also be very useful in identifying subtle differences in the QRS complexes that can be important clues to the mechanism of tachycardia. For example, in orthodromic AV re-entrant circus tachycardia (with the antegrade limb being the AV node and retrograde limb being an AV accessory pathway), preexcitation will be lost during tachycardia but may be present during normal sinus rhythm (though with concealed accessory pathways in which there is no antegrade conduction, there will not ever be ventricular preexcitation). Carotid massage can also terminate SVTs but is less useful diagnostically if not performed during simultaneous 12-lead ECG. A tilt table test is not a useful test in patients with palpitations or clearly documented tachycardia, even with syncope; it is useful only in neurocardiogenic syncope. A 12-lead ECG during the tachycardia is very useful and should be obtained whenever possible; however, more information will be obtained from a 12-lead ECG during adenosine administration. An echocardiogram might be useful in excluding valvular or structural heart disease, depending on the history and physical examination, but it does not need to be performed during the tachycardia. Similarly, a nuclear stress test is indicated only if there is suspicion of coronary artery disease, which is rarely the primary cause of an SVT.

5. What features from the history are most important in distinguishing neurocardiogenic syncope from seizure disorder?

- A. Post-episode confusion lasting more than 5 minutes
- B. Jerking movements of limbs during the episode
- C. Triggered by pain
- D. A prodrome of nausea and sweatiness
- E. A, C, and D

Answer: E See Table 62-2 and Neurocardiogenic Syncope and Related Syndromes. Because neurocardiogenic syncope commonly presents in young, otherwise healthy individuals, the differential diagnosis often involves a new seizure disorder. Several important historical features and the appearance of the patient during the syncopal episode (when observed by a bystander) can be very useful in distinguishing neurocardiogenic syncope from a seizure disorder. In seizure disorders, a postictal confusion period lasting more than 5 minutes is common; in neurocardiogenic syncope, by comparison, disorientation rapidly resolves within a 1 or 2 minutes upon regaining consciousness. In a patient who has had a cardiac arrest (distinct from syncope), the period of confusion can last very long if the patient has suffered anoxic brain injury; however, anoxic brain injury is very uncommon in neurocardiogenic syncope. Jerking movements of the limbs can be confused with myoclonic movements that are common in neurocardiogenic syncope, so these movements are not helpful in

distinguishing between seizure disorder and neurocardiogenic syncope. Neurocardiogenic syncope is often triggered by pain or prolonged standing; commonly one can elicit a history of syncope or pre-syncope with abdominal cramping, phlebotomy, or other painful stimuli. Seizures are not usually triggered by pain. Although seizure disorders can sometimes be associated with prodromes, they commonly involve sensory auras. Neurocardiogenic syncope often is preceded by reproducible prodromes of nausea and sweatiness, which are triggered by the heightened parasympathetic tone that causes the acute drop in blood pressure and heart rate and which can persist after the episode.

Ch / 63 APPROACH TO CARDIAC ARREST AND LIFE-THREATENING ARRHYTHMIAS

1. Which of the following electrocardiogram (ECG) patterns at first contact with a cardiac arrest victim has the lowest probability of survival?

- A. Asystole
- B. Polymorphic ventricular tachycardia
- C. Pulseless ventricular tachycardia
- D. Pulseless electrical activity
- E. Ventricular fibrillation

Answer: A Cardiac arrest victims with shockable rhythms (B, C, and E) have higher probabilities of survival than pulseless electrical activity or asystole (A and D). Asystole may appear after delayed or prolonged treatment of ventricular tachyarrhythmias or fibrillation, or as a primary mechanism in patients with preexisting advanced heart disease or terminal noncardiac diseases. In either situation, survival is low. Pulseless electrical activity also has a low probability of survival because it generally takes longer to restore circulation in nonshockable rhythms, but survival is better than for asystole.

2. A 35-year-old man suffered a cardiac arrest while running a marathon and was found to be in ventricular fibrillation by emergency rescue personnel. He had had no prior history of chest pain or palpitations. A structural cause for his cardiac arrest is identified at postmortem examination. Which of the following disorders is the most likely cause of his cardiac arrest?

- A. Aortic stenosis
- B. Congenital long QT interval syndrome
- C. Coronary atherosclerosis
- D. Hypertrophic cardiomyopathy
- E. Nonischemic dilated cardiomyopathy

Answer: C The less common cardiac disorders such as hypertrophic cardiomyopathy and the inherited arrhythmia syndromes are more common causes of sudden cardiac arrest than coronary artery disease in the adolescent and younger adult population. However, coronary atherosclerosis emerges as the most common cause in people older than 30 to 35 years.

3. A 45-year-old man comes to the emergency department because of the sudden onset of a tachycardia associated with mild lightheadedness. Initial ECG shows a regular wide QRS tachycardia at a rate of 165 beats per minute; blood pressure is 126/82 mm Hg. He denies a prior history of heart disease, and no information is available on his left ventricular function. Which of the following drugs should not be used as initial management of this arrhythmia?

- A. Adenosine
- B. Digoxin
- C. Metoprolol
- D. Procainamide
- E. Verapamil

Answer: E Verapamil given intravenously causes clinically relevant myocardial depression in patients with left ventricular dysfunction due to structural heart disease. Therefore, regardless of the mechanism of a tachycardia, intravenous verapamil should not be used in the absence of prior knowledge that left ventricular function is normal.

4. A 72-year-old woman with a prior myocardial infarction and an ejection fraction of 40% collapsed in a shopping mall. A bystander found her to be pulseless and began “compression-only” cardiopulmonary resuscitation (CPR). An automated external defibrillator was deployed approximately 3 minutes after collapse and demonstrated ventricular fibrillation. An initial 200-J biphasic shock failed to restore sinus rhythm. Which of the following should be the next step in management?

- A. Deliver a second 200-J biphasic shock immediately.
- B. Inflate the lungs with mouth-to-mouth respirations twice and then deliver a second shock.
- C. Resume CPR for five cycles of 15 : 2 compressions/ventilations before delivering another shock.
- D. Deliver a precordial thump, and recheck the rhythm.
- E. Resume CPR immediately and deliver another 200-J biphasic shock after 2 minutes of chest compressions.

Answer: E Based on the concept of maximizing chest compressions for preserving organ viability, the prior strategy of delivering three successive shocks before resuming CPR has been replaced by the guideline that CPR should be resumed after a single shock that fails to restore circulation. CPR should be continued using the compression-only technique for 2 minutes before the second shock is delivered.

5. For a cardiac arrest patient who is in ventricular fibrillation and has failed multiple attempts to restore circulation despite CPR, attempted defibrillation, and epinephrine, which of the following intravenous medications should be tried next?

- A. Amiodarone
- B. Lidocaine
- C. Magnesium sulfate
- D. Procainamide
- E. Propranolol

Answer: A After failure to restore sinus rhythm by 3 cycles of defibrillator shocks and chest compressions, including the administration of epinephrine or vasopressin, a randomized clinical trial has demonstrated that amiodarone intravenously is more effective than lidocaine for restoring circulation, usually with subsequent shocks. Lidocaine is an acceptable alternative if the ventricular fibrillation (VF) event is due to an acute ischemic syndrome, and magnesium sulfate is preferable when VF is due to prolonged QT interval syndrome. Procainamide can be tried after amiodarone and/or lidocaine has failed, but it is unlikely to be of benefit.

Ch / 67 ARTERIAL HYPERTENSION

1. An 80-year-old woman makes an appointment for initial evaluation of hypertension, which was detected by her orthopedist. She has enjoyed excellent health her entire life and remains very active. She has never been treated for hypertension. Her only other medical issue is occasional sciatica from lumbar degenerative disc disease. Her only medication is vitamin D with calcium. In your office, her seated blood pressure averages 200/90 mm Hg and heart rate is 77 beats per minute. There are no significant orthostatic changes in her blood pressure or heart rate. Her complete metabolic panel and resting electrocardiogram are normal. Which of the following is the most appropriate course of action?

- A. Initiate antihypertensive therapy by prescribing a thiazide-type diuretic.
- B. Schedule a follow-up visit in 2 weeks to repeat the blood pressure measurement to confirm the diagnosis of hypertension before prescribing medication.
- C. Order an ambulatory blood pressure monitor.
- D. Send the patient to the emergency department for treatment of hypertensive urgency.
- E. Initiate antihypertensive therapy with an angiotensin-converting enzyme (ACE) inhibitor plus a thiazide because the patient has stage 2 hypertension.

Answer: C White coat hypertension and masked hypertension are so common in elderly patients that the office blood pressure will lead to overtreatment or undertreatment of blood pressure in 3 out of 4 patients. Because this patient has no evidence of symptomatic or asymptomatic target organ damage, you suspect white coat hypertension; the best option is to send the patient home with a 24-hour ambulatory blood pressure monitor, which she should wear until she returns to your office the next day. Her out-of-office daytime blood pressure averages 141/55 mm Hg, and her sleeping blood pressure averages 143/57 mm Hg. Normal awake daytime blood pressure is less than 135/85 mm Hg, and normal nighttime sleeping blood pressure is less than 120/70 mm Hg. Thus, this patient has a brisk white coat reaction superimposed on very mild daytime hypertension. She also has nocturnal hypertension (no dip), which merits gentle medication therapy. There is no indication that the patient has a hypertensive urgency. It is not appropriate to institute medication therapy before confirming the diagnosis of hypertension, but a second office visit is almost certainly going to evoke another white coat reaction. (Franklin SS, Thijs L, Hansen TW, et al. Significance of white-coat hypertension in older persons with isolated systolic hypertension: a meta-analysis using the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes population. *Hypertension*. 2012;59:564-571.)

2. A 52-year-old man has chronic hypertension and has had type 2 diabetes for 8 years. He is treated with diet and metformin. You are treating his hypertension with lisinopril/hydrochlorothiazide 40/25 mg daily and amlodipine 5 mg daily. On this regimen, he has a mild cough. His office blood pressure averages 145/91 mm Hg, and his home blood pressures (which he recorded as you requested) are between 133/83 and 151/92 mm Hg, with an average of 140/87 mm Hg. His basic metabolic panel includes: Na 133 mEq/L, K 3.7 mEq/L, CO₂ 25 mmol/L, Cl 100 mmol/L, creatinine 1.2 mg/dL, BUN 22 mg/dL. His eGFR is 65 mL/min/1.73 m². His fasting glucose level is 165 mg/dL with a hemoglobin A1C of 7.5%. A spot morning urine albumin-to-creatinine ratio is 350 mg/g. Which of the following is the most appropriate next step?

- A. Add an angiotensin receptor blocker (ARB) to the current regimen to reduce the patient's proteinuria and slow the progression of his diabetic nephropathy.
- B. Add the new direct renin inhibitor aliskiren to the current regimen to reduce the patient's proteinuria and slow the progression of diabetic nephropathy.
- C. Add metoprolol to the current regimen to improve the control of his hypertension.
- D. Replace lisinopril/hydrochlorothiazide with an ARB and start controlled-release carvedilol 20 mg daily.
- E. Maintain the current regimen.

Answer: D The patient has early diabetic nephropathy with proteinuria and also has an angiotensin-converting enzyme (ACE) inhibitor cough. He is on a good blood pressure regimen with three first-line drugs. However, his blood pressure is not yet at goal (office blood pressure either less than 140/90 mm Hg or less than 130/80 mm Hg by different current guidelines; home blood pressure less than 135/85 mm Hg), and his hemoglobin A1C level is elevated. The best option is to replace the ACE inhibitor with an ARB and to add a vasodilating β -blocker (such as carvedilol), which will not exacerbate his hyperglycemia. His hemoglobin A1C level may improve if his hypertension can be controlled without a thiazide diuretic; if not, low-dose chlorthalidone (6.25 mg daily to start and titrate) would be the best option. Dual renin-angiotensin system blockade with either any combination of an ARB plus ACE inhibitor, or an ACE inhibitor plus aliskiren, increases complications without providing benefit compared with either an ACE inhibitor alone or an ARB alone and should not be used. (Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk [the ONTARGET study]: a multicentre, randomised, double-blind, controlled trial. *Lancet*. 2008;372:547-553; Parving HH, Brenner BM, McMurray JJ, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med*. 2012;367:2204-2213.)

3. A 60-year-old male bus driver transfers to your care with a chief complaint of resistant and labile hypertension and an inability to return to work until you provide medical clearance. His current regimen is hydrochlorothiazide 25 mg daily, metoprolol XL 100 mg daily, and clonidine 0.2 mg twice daily, with an extra dose of 0.2 mg if his systolic blood pressure is above 180 mm Hg. His office blood pressure is 189/88 mm Hg with a heart rate of 50 seated, and 195/92 mm Hg with a heart rate of 50 standing. The patient's home blood pressure readings range anywhere from 85/55 to 225/125 mm Hg. He is generally lethargic, often dizzy, and feels anxious when his blood pressure spikes. What is the most likely issue and best course of action?

- A. Medication nonadherence: draw drug blood levels and confront the patient if they are low.
- B. Clonidine rebound: taper clonidine gradually while starting a calcium-channel blocker (amlodipine 5 mg daily) and an angiotensin receptor blocker (telmisartan), and replace hydrochlorothiazide with chlorthalidone 25 mg daily.
- C. Pheochromocytoma: measure plasma metanephrines and start an α -blocker (doxazosin 8 mg twice daily).
- D. Dysautonomia: refer the patient to a neurologist for autonomic function testing
- E. Resistant hypertension: refer the patient to a hypertension specialist for consideration of renal denervation

Answer: B This patient likely has pseudoresistant hypertension owing to an inadequate medical regimen with clonidine rebound. His blood pressure is rebounding in your office (the appointment is 8 hours after his morning dose of clonidine). The appropriate course of action is to reduce the clonidine dose to 0.1 mg given 4 times daily, so as to prevent rebound between doses, for 1 or 2 weeks, next to reduce the dose to 0.05 mg four times daily for another week, and finally to stop clonidine altogether and never restart it. At the same time, the patient should be started on the three first-line drugs for hypertension recommended by almost all current guidelines: a long-acting calcium-channel blocker, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and a thiazide-type diuretic (chlorthalidone). The patient's heart rate of 50 beats per minute indicates that he is taking his metoprolol, which is not a first-line drug for hypertension. Metoprolol should be tapered gradually later if he has no indication, such as coronary artery disease or heart failure, for a β -blocker. There is nothing in his history to suggest a pheochromocytoma, which is far less common than clonidine rebound, which itself can cause false-positive metanephrine screening. There is no orthostatic hypotension to suggest autonomic failure. Renal denervation is an exciting potential percutaneous intervention for true drug-resistant hypertension, which he does not have.

4. A 57-year-old African American man has a progressive increase in his serum creatinine from 1.3 to 1.8 mg/dL over the past 2 years, accompanied by microalbuminuria and left ventricular hypertrophy with repolarization abnormalities ("strain") by electrocardiogram despite having office blood pressures consistently averaging 130/65 mm Hg on the following regimen: furosemide 40 mg daily, atenolol 50 mg daily, and amlodipine 5 mg daily. He has no diabetes and quit smoking 15 years ago. What would you recommend?

- A. Order a 24-hour ambulatory blood pressure monitor.
- B. Continue current medications and refer the patient to a nephrologist for renal biopsy.
- C. Replace furosemide with chlorthalidone 25 mg daily, taper off atenolol, and add an angiotensin receptor blocker (ARB).
- D. A, B, and C
- E. A and C

Answer: E This patient likely has masked and nocturnal hypertension, which can be documented by ambulatory blood pressure monitoring. Masked hypertension and nocturnal hypertension are particularly common in chronic kidney disease, presumably owing to sympathetic overactivity, and they increase the risk for left ventricular hypertrophy and cardiovascular death. His current regimen is not appropriate. An ARB is indicated for renal protection in chronic kidney disease with microalbuminuria and for regression of left ventricular hypertrophy. Once-daily furosemide is not an effective antihypertensive medication because of its short half-life; chlorthalidone is a much better diuretic for 24-hour blood pressure control and should be effective in stage 2 or 3 chronic kidney disease. Furthermore, amlodipine should not be given without an ARB or angiotensin-converting enzyme inhibitor in the setting of chronic kidney disease. (Fagard RH, Celis H, Thijs L, et al. Regression of left ventricular mass by antihypertensive treatment: a meta-analysis of randomized comparative studies. *Hypertension*. 2009;54: 1084-1091.)

5. A 59-year-old woman with difficult-to-control hypertension just had a nuclear medicine stress test as part of her annual executive physical elsewhere. However, because of her uncontrolled hypertension, the cardiologist considered renovascular hypertension and ordered a renal computed tomographic angiogram, which showed a 75% stenosis of the proximal left renal artery and a small plaque in her right renal artery. Both of her kidneys were normal in size and function. Her office blood pressure is now averaging 150/70 mm Hg on hydrochlorothiazide 25 mg daily, lisinopril 40 mg daily, metoprolol XL 25 mg daily, and diltiazem CD 360 mg daily. She has a low-density lipoprotein cholesterol level of 139 mg/dL but does not want to take a statin because she is concerned about potential side effects. She is overweight (body mass index of 29) and does not exercise regularly. The patient trusts your judgment and wants to know if she should undergo renal angioplasty for renovascular hypertension. What would you recommend?

- A. Renal angiography and balloon angioplasty with stenting
- B. Intensify her blood pressure by replacing hydrochlorothiazide with chlorthalidone, metoprolol with nebivolol, and diltiazem CD with amlodipine.
- C. A low sodium diet, high in fruits and vegetables, combined with a regular moderately intense aerobic exercise regimen at her company's gym for 40 minutes per session, 4 to 5 days per week
- D. Strongly encourage statin therapy.
- E. B, C, and D

Answer: E Stenting is no more effective than intensive medical therapy for renal artery stenosis and is accompanied by significant complications. Because her kidneys are of equal and normal size on computed tomographic images, the unilateral renal artery stenosis is unlikely to be severe enough to cause substantial renal ischemia. The best approach to prevent or delay progression of her atherosclerotic renal artery stenosis is to encourage lifestyle recommendations, intensify her antihypertensive regimen with stronger and longer lasting medication, and start statin therapy. (Cooper CJ, Murphy TP, Cutlip DE, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. *N Engl J Med* 2014;370:13-22; Wheatley K, Ives N, Gray R, et al. Revascularization versus medical therapy for renal-artery stenosis. *N Engl J Med*. 2009;361:1953-1962.)

Ch / 68 PULMONARY HYPERTENSION

1. A 63-year-old man presents with a 3-year history of progressive dyspnea on exertion. He is now unable to walk more than 100 feet without becoming dyspneic. On physical examination, he has a parasternal lift, a loud pulmonic component to the second heart sound, a tricuspid regurgitant murmur, a pulmonary vascular bruit, and 1+ lower extremity edema. His echocardiogram demonstrates normal left ventricular function, moderate right ventricular enlargement and dysfunction, and an estimated right ventricular systolic pressure of 75 mm Hg. Which is the most likely diagnosis?

- A. Heart failure with preserved ejection fraction
- B. Chronic thromboembolic pulmonary hypertension
- C. Sleep-disordered breathing
- D. Idiopathic pulmonary arterial hypertension
- E. Pulmonary arterial hypertension due to an atrial septal defect

Answer: B The presence of a pulmonary vascular bruit on physical examination is specific to chronic thromboembolic pulmonary hypertension. Pulmonary vascular bruits arise from turbulent flow through partially obstructed pulmonary arteries. A history of a prior acute pulmonary embolism is absent in about 50% of patients who are diagnosed with chronic thromboembolic pulmonary hypertension.

2. A 35-year-old woman presents with a 1-year history of progressive dyspnea. She has been treated with bronchodilators but has not improved. She has symptoms of dyspnea and chest discomfort with modest exertion. Her physical examination reveals a right ventricular heave, a loud pulmonic component to her second heart sound, and a 2/6 tricuspid regurgitant murmur. Her electrocardiogram demonstrates right axis deviation. What is the most appropriate next study in her evaluation?

- A. Exercise treadmill test
- B. Echocardiogram
- C. Pulmonary function tests
- D. High-resolution chest computed tomography
- E. Right-sided heart catheterization

Answer: B This patient has typical symptoms of pulmonary hypertension, and her physical examination is consistent with that diagnosis. The most appropriate next study is an echocardiogram to assess the size and function of her right-sided heart chambers, to estimate her right ventricular systolic pressure, and to evaluate her for other potential cardiac abnormalities that may contribute to pulmonary hypertension. Although she has exertional chest discomfort, coronary artery disease is unlikely to be the cause on the basis of her age and the findings on physical examination. Further evaluation of parenchymal lung disease may be appropriate at some point, but on the basis of her symptoms and physical examination findings, pulmonary hypertension is more likely.

3. A 32-year-old woman is diagnosed with idiopathic pulmonary arterial hypertension. On presentation, she had dyspnea with minimal exertion, exertional lightheadedness, and evidence of right-sided heart failure with 2+ lower extremity edema. Her right-sided heart catheterization revealed a mean pulmonary artery pressure of 60 mm Hg, right atrial pressure of 21 mm Hg, pulmonary capillary wedge pressure of 7 mm Hg, and cardiac index of 1.8 L/min/m². What is the most appropriate initial therapy for her?

- A. Macitentan
- B. Sildenafil
- C. Riociguat
- D. Intravenous epoprostenol
- E. Inhaled iloprost

Answer: D This patient has advanced symptoms (functional class IV), signs of right-sided heart failure, and hemodynamics that portend a poor prognosis. Intravenous epoprostenol is the only pulmonary arterial hypertension therapy that has a grade A recommendation for patients with functional class IV symptoms. The other agents may be appropriate therapy for patients with less advanced symptom.

4. Which of the following are accepted treatment goals for patients with pulmonary arterial hypertension?

- A. Functional class I or II symptoms
- B. Cardiac index > 2.5 L/min/m²
- C. Nearly normal right ventricular function on imaging study
- D. Normal brain natriuretic peptide
- E. All of the above

Answer: E Treatment goals of pulmonary arterial hypertension have been established primarily from observational studies. Improving right ventricular function and consequently symptoms and exercise tolerance portends a better prognosis, regardless of which therapies have been used to obtain the goal. Patients with pulmonary arterial hypertension should be observed with reassessment of symptoms, exercise tolerance, and right ventricular function on a periodic basis. Combination therapy may be required to achieve treatment goals.

Ch / 69 CONGENITAL HEART DISEASE IN ADULTS

1. A 43-year-old man presents to the emergency department with a history of tetralogy of Fallot and syncope. He currently feels well. He has no chest pain. His 12-lead electrocardiogram (ECG) shows a right bundle branch block and three premature ventricular ectopic beats. What is your plan with respect to this patient's disposition?
- A. You admit him to a monitored bed and consult a cardiologist with expertise in adult congenital heart disease.
 - B. You check his old ECG and find that this one is unchanged, so you send him home to follow up with his cardiologist as an outpatient.
 - C. You consult the neurologist because you are worried that given his history, he may have had a seizure.
 - D. You admit him for a cardiac catheterization because you know that tetralogy of Fallot may be associated with an anomalous coronary artery.
 - E. None of the above

Answer: A Patients with tetralogy of Fallot have up to a 5% risk of sudden cardiac death. Therefore, the presentation of syncope should always prompt an admission for monitoring to exclude a malignant ventricular arrhythmia. In addition, consultation with a congenital heart disease expert should always be initiated to exclude any new or progressive hemodynamic abnormality, such as pulmonary regurgitation that may require intervention. Although patients with tetralogy of Fallot may have coronary artery anomalies, syncope always warrants monitoring, and unexplained syncope may warrant an electrophysiology study.

2. A 50-year-old woman presents with shortness of breath to your office. One year ago, she had a moderate-sized myocardial infarction, for which she underwent successful dilation of a midcircumflex lesion with no complications. She denies angina. You examine her and find that her blood pressure is 140/90 mm Hg and her heart rate is 80 beats per minute. She has no evidence of systemic or pulmonary venous congestion. She has a positive hepatojugular reflux and a widely split second heart sound. She has an incomplete right bundle branch block on the ECG with no ischemic changes. You order an echocardiogram and find that she has an enlarged right side of the heart, which was not seen on her last echocardiogram 1 year ago. What investigations are you interested in?
- A. You review the echocardiogram looking for evidence of a right-to-left shunt at the atrial level.
 - B. You order a cardiac catheterization to exclude disease of the right coronary artery.
 - C. You review the echocardiogram looking for evidence of a left-to-right shunt at the atrial level.
 - D. You order an exercise echocardiogram to see if there are new wall motion anomalies.
 - E. None of the above

Answer: C This is a classic presentation of an atrial septal defect that becomes symptomatic when diastolic dysfunction from acquired cardiovascular disease reduces left ventricular compliance, increases left ventricular end-diastolic pressure and left atrial pressure, and increases left-to-right shunting. Patients who have an atrial septal defect may be asymptomatic into their fourth and fifth decade until a condition such as hypertension, mitral regurgitation, aortic valve disease, cardiomyopathy, or myocardial infarction decreases left ventricular compliance and increases left-to-right shunting. Atrial septal defects can be easily missed on echocardiography if they are not specifically sought. The patient is not cyanotic, so an increase in right-to-left shunting may not be found. In addition, although the patient has coronary disease, an echocardiogram would still be the best initial test to evaluate ventricular function.

3. A 20-year-old man is referred to you for unexplained hypertension. He otherwise feels well. You notice he has a well-developed torso, and he tells you he lifts weights. His blood pressure is 150/90 mm Hg in both arms. He has a sustained apical impulse and a systolic ejection click. His ECG shows left ventricular hypertrophy. What is in your management plan?

- A. You order an echocardiogram to exclude a bicuspid aortic valve and initiate β -blocker therapy.
- B. You order an evaluation for renal artery stenosis and initiate therapy with an angiotensin-converting enzyme inhibitor.
- C. You are unsure of what to do so you refer him to a local cardiologist.
- D. You order an echocardiogram to exclude aortic coarctation, you order a 24-hour blood pressure monitor to confirm his hypertension, and you give him a follow-up appointment in 2 weeks with the intention of starting antihypertensive medication.
- E. None of the above

Answer: D The finding of unexplained hypertension in a young man should always prompt a careful clinical examination to detect a possible brachial-to-femoral pulse delay and an echocardiogram to exclude aortic coarctation. Because blood flow is decreased in the lower extremities, these patients often have small hips relative to a well-developed torso. A significant portion of patients also have a bicuspid aortic valve, but it does not explain the hypertension. Because aortic coarctation is a reversible cause of hypertension, it is important to look for it and to address its complications.

4. A 45-year-old woman is referred to you from another general internal medicine practice where the internist is retiring. She is in a wheelchair with an oxygen tank and nasal prongs. She has bluish discoloration of her skin and clubbing of her fingernails. She explains that she has a heart condition and is here to have her monthly phlebotomy. What should you do?
- A. You order the phlebotomy, and you have her come back in 1 month.
 - B. You review her medical record, take a history for symptoms of hyperviscosity, exclude dehydration, and order serum iron studies.
 - C. You make sure she does not smoke and consult a pulmonologist to determine if she needs the oxygen.
 - D. You go through the medical record and wonder why she has not had an operation for her cyanosis. You consult the nearest adult congenital heart specialist.
 - E. All of the above

Answer: B Patients with cyanotic congenital heart disease often undergo unnecessary phlebotomy. This clinical scenario requires a careful history to establish the presence or absence of hyperviscosity, which is an indication for phlebotomy in the absence of iron deficiency, and a discussion of the need or lack thereof for phlebotomy. Patients are often resistant initially; but after their hemoglobin levels stabilize and in the absence of iron deficiency, they often feel much better.

5. A 25-year-old woman with a bicuspid aortic valve and mild aortic regurgitation consults you before visiting her dentist. She requests a prescription for antibiotic prophylaxis before undergoing extensive dental cleaning. How do you respond?
- A. You give her the prescription as she requests.
 - B. You call the dentist, who confirms the request, and you give her the prescription.
 - C. You take a careful history to be sure she is not allergic to penicillin.
 - D. You explain that antibiotic prophylaxis is no longer required for dental procedures and write her dentist a confirmatory letter.
 - E. None of the above

Answer: D Bacterial endocarditis prophylaxis is no longer recommended for isolated native valve lesions, such as a bicuspid aortic valve, in the absence of surgery or a previous episode of infective endocarditis. It is important to understand the rationale for the change in guidelines. It is not that infective endocarditis does not occur in patients with isolated lesions; rather, antibiotic prophylaxis cannot be shown to reduce the risk of this complication, especially because bacteremias after routine dental procedures are no worse than after brushing one's teeth. This situation requires careful discussion and accurate transmission of information to the patient.

1. In comparison to patients with ST segment elevation myocardial infarction (STEMI), the mortality rates for subjects with non-ST segment elevation acute coronary syndrome (NSTEMI) are
- A. Lower in-hospital, similar at 6 months, and higher long term
 - B. Similar in-hospital, at 6 months, and long term
 - C. Higher in-hospital, 6 months later, and long term
 - D. Lower in-hospital, 6 months later, and long term
 - E. Higher in-hospital, then similar at 6 months as well as long term

Answer: A Large observational cohort studies have demonstrated that mortality rates with NSTEMI are lower in-hospital, similar at 6 months, and actually higher long term, such that 4 years after the event, the mortality for those with NSTEMI is twice that of survivors of STEMI. As a result, the chosen management strategy for patients with NSTEMI is designed to minimize the chance of recurrent ACS or death, both acutely and chronically.

2. The acute coronary syndrome (ACS) patient with the following criteria is considered to be at high risk and, unless it is contraindicated, should be managed with aggressive medical therapy as well as coronary angiography and revascularization if it is anatomically appropriate.
- A. Age younger than 65 years, diabetes mellitus, and a history of smoking
 - B. Three or more Thrombolysis in Myocardial Infarction (TIMI) risk variables, age older than 75 years, and a positive serum troponin concentration
 - C. ST segment depression, positive serum troponin concentration, and male gender
 - D. Previous coronary artery bypass grafting or percutaneous coronary intervention, diabetes mellitus, and hypertension
 - E. Heart rate above 100 beats per minute, T wave inversions in multiple leads, and more than three TIMI risk variables

Answer: B Meta-analyses of all randomized trials of management of subjects with NSTEMI have demonstrated that those with more than three TIMI risk variables, age older than 75 years, and a positive serum troponin concentration are at high risk of a recurrent ischemic event (myocardial infarction, recurrent ischemia, or death) and obtain a substantial benefit when they are managed invasively (intensive medical therapy and coronary angiography/ revascularization within 72 hours of hospitalization).

3. To promote plaque stabilization, all patients with NSTEMI should receive the following before and after hospital discharge.
- A. Rosuvastatin, 10 mg daily
 - B. Simvastatin, 40 mg daily
 - C. Atorvastatin, 40 mg daily
 - D. Pravastatin, 40 mg daily
 - E. Atorvastatin, 80 mg daily

Answer: E Randomized trials have shown that high-dose atorvastatin (80 mg daily), begun in-hospital and continued indefinitely, effectively reduces the incidence of recurrent ischemic events. Lower doses of the same drug and rosuvastatin have not been assessed in this population of patients. Simvastatin 40 mg is no more efficacious than placebo and pravastatin 40 mg is inferior to high-dose atorvastatin in NSTEMI patients.

4. The anticoagulant of choice for the subject with heparin-induced thrombocytopenia who is referred for coronary arteriography is
- A. Low-molecular-weight heparin
 - B. Dextran
 - C. Fondaparinux
 - D. Bivalirudin
 - E. High-dose aspirin and clopidogrel

Answer: D In the subject with heparin-induced thrombocytopenia, any form of heparin is contraindicated (hence, low-molecular-weight heparin is an incorrect choice). Intensive high-dose antiplatelet therapy (aspirin and clopidogrel) is of no additional benefit. Dextran is of no benefit at all. Because an increased incidence of catheter-related thrombosis has been reported after fondaparinux treatment, it is not recommended for the patient who is likely to undergo coronary angiography.

Ch / 73 ST SEGMENT ELEVATION ACUTE MYOCARDIAL INFARCTION AND COMPLICATIONS OF MYOCARDIAL INFARCTION

1. The recommended duration of antiplatelet therapy with a P2Y12 inhibitor after drug-eluting stent placement for ST segment elevation myocardial infarction (STEMI) is
- A. 1 month
 - B. 3 months
 - C. 6 months
 - D. 1 year
 - E. Indefinitely

Answer: D Early discontinuation of P2Y12 inhibition is associated with an increased risk of stent thrombosis. A favorable benefit-to-risk ratio of longer-term/indefinite therapy has not been proved.

2. Which of the following scenarios should *not* be considered for immediate reperfusion therapy (e.g., primary percutaneous coronary intervention) in a patient presenting with suspected acute coronary syndrome?
- A. ST elevation >2 mm in precordial leads or >1 mm in limb leads
 - B. New-onset left bundle branch block
 - C. Resuscitated ventricular fibrillation (VF) arrest
 - D. ST depression in precordial leads and ST elevation in supplemental leads V7 to V9
 - E. None of the above (i.e., all of the above are correct)

Answer: E A and B are classic indications. VF in the setting of suspected acute coronary syndrome/STEMI is also an indication for rapid percutaneous coronary intervention. D represents a posterior myocardial infarction, which typically is caused by occlusion of the left circumflex coronary artery and should be treated as STEMI.

3. Newly available high-sensitivity, cardiac-specific troponin assays promise the following diagnostic advantages *except*
- A. Increased diagnostic sensitivity
 - B. Increased diagnostic specificity
 - C. Reduced time to diagnostic rise in troponin levels after the onset of pain
 - D. All of the above
 - E. None of the above

Answer: B There are many non–myocardial infarction causes of troponin elevation; the newer, high-sensitivity assays can detect circulating troponin at baseline in a higher percentage of all patients, including those without acute coronary syndromes. As a result, the assays increase sensitivity, reduce time to diagnosis, and reduce specificity, thereby necessitating improved clinical judgment in their interpretation.

4. An implantable cardioverter-defibrillator (ICD) should be considered before discharge for which of the following STEMI patients?

- A. STEMI presenting with VF (successfully resuscitated)
- B. STEMI with sustained ventricular tachycardia (VT)/VF occurring more than 48 hours after presentation
- C. STEMI with ongoing runs of nonsustained VT on telemetry
- D. STEMI with predischARGE ejection fraction of 30% or less, regardless of rhythm
- E. All of the above

Answer: B The risk of recurrent VT/VF is generally low for early (ischemic) VF, given current reperfusion and antithrombotic therapies. In contrast, convalescent presentation (at >48 hours) of sustained VT/VF carries a high risk of recurrence, and early ICD implantation should be considered. For patients with low ejection fractions, clinical trials (and Medicare reimbursement rules) support a waiting period of at least 40 days after myocardial infarction before considering an ICD. For nonsustained VT, implantation of an ICD is generally not indicated except in patients who have a reduced left ventricular ejection fraction and in whom it is induced on an electrophysiologic study.

Ch / 74 INTERVENTIONAL AND SURGICAL TREATMENT OF CORONARY ARTERY DISEASE

1. Bare metal coronary stents reduce restenosis by

- A. providing a semirigid scaffold that resists vessel recoil and remodeling.
- B. inhibiting intimal proliferation.
- C. reducing thrombus formation.
- D. increasing blood flow within the coronary artery.
- E. reducing vessel spasm.

Answer: A Bare metal stents use mechanical force to hold a vessel open. They do not reduce vessel spasm or thrombus formation. Stents increase intimal proliferation. Although stents increase vessel blood flow, the increased blood flow does not influence restenosis rates.

2. Compared with medical therapy, percutaneous coronary intervention

- A. reduces the mortality rate in patients with stable angina.
- B. reduces costs associated with medical care.
- C. reduces the mortality rate in patients experiencing an acute myocardial infarction.
- D. decreases myocardial infarction in patients with stable coronary artery disease.
- E. reduces hospitalization rates.

Answer: C In randomized trials, coronary stents have been shown to reduce mortality rates compared with medical therapy alone in patients experiencing an acute myocardial infarction (MI). In patients with stable coronary disease, stents reduce angina but do not reduce death, MI, hospitalization rates, or costs.

3. Randomized trials comparing bypass surgery to coronary stents

- A. found an increased late stroke rate in patients receiving bypass surgery.
- B. found less angina in patients who underwent bypass surgery.
- C. found higher MI rates in patients undergoing stenting.
- D. demonstrated improved late outcomes in patients with diabetes undergoing stenting.
- E. demonstrate improved survival in patients with extensive complex coronary disease

Answer: E In randomized trials, bypass surgery has been shown to reduce mortality rates compared with coronary stenting in patients with three-vessel, complex coronary disease. Stroke rates are higher in bypass patients early after surgery, but stroke rates are similar at later follow-up. Rates of MI and angina are equivalent on long-term follow-up. Patients with diabetes who have multivessel disease have better long-term outcomes with bypass surgery.

4. What is an important component of the coronary bypass surgery operation for increasing life expectancy?

- A. Saphenous vein graft to the left anterior descending (LAD) coronary artery
- B. Radial graft to the right coronary artery
- C. Minimally invasive surgery
- D. Left internal mammary artery graft to the LAD coronary artery
- E. The right gastroepiploic graft to the right coronary artery

Answer: D Although no randomized trials have examined the impact of the left internal mammary artery to LAD graft, many observational comparative studies have established the long-term survival benefit of this surgical strategy.

5. What is the most common indication for recommending bypass surgery for patients with stable angina in preference to other treatment options is?

- A. To prevent myocardial infarction
- B. To increase exercise capacity
- C. To improve life expectancy
- D. To decrease the side effects of optimal medical therapy

Answer: C Advances in medical therapy and in percutaneous interventions have commonly been successful in controlling symptoms of angina, so coronary bypass surgery is rarely needed to treat symptoms that are unresponsive to alternative management strategies. However, for patients with severe coronary artery disease, bypass surgery is the form of therapy that has been most clearly shown to improve life expectancy. The most common indications for CABG are in anatomic and clinical situations in which it offers a survival benefit.

Ch / 75 VALVULAR HEART DISEASE

1. Each of the following findings indicates severe valvular heart disease except

- A. in mitral stenosis, the S2 opening snap interval is 0.06 seconds.
- B. in aortic stenosis, there is a harsh systolic murmur peaking in mid-systole.
- C. in aortic stenosis, there is a soft single second sound.
- D. in aortic regurgitation, an Austin Flint murmur is heard.
- E. in mitral regurgitation, an S3 is heard.

Answer: B The murmur of severe aortic stenosis peaks late in systole, not in midsystole. An S2-OS interval of 0.06 sec is short, indicating high left atrial pressure and severe mitral stenosis. Severe aortic regurgitation impinges on the mitral valve, thereby causing an Austin Flint murmur. A severely calcified and stenotic aortic valve produces little sound when it closes, so S2 will be soft and single.

2. Pick the best choice regarding the hemodynamic overload of valvular heart disease.

- A. Aortic regurgitation places a pure volume overload on the left ventricle.
- B. Aortic stenosis produces a combined pressure and volume overload on the left ventricle.
- C. Aortic regurgitation places a combined pressure and volume overload on the left ventricle.
- D. Mitral regurgitation places a combined pressure and volume overload on the left ventricle.
- E. Tricuspid regurgitation places a combined pressure and volume overload on the right ventricle.

Answer: C The increased total stroke volume in aortic regurgitation increases systolic blood pressure, thereby placing a combined pressure and volume overload on the left ventricle. Whereas aortic stenosis causes a pure left ventricle pressure overload, mitral and tricuspid regurgitation place a pure volume overload on the left ventricle and right ventricle respectively.

3. Indications for valve surgery or other valve intervention include all but which of the following?

- A. A patient with syncope and an aortic valve area of 0.9 cm².
- B. An asymptomatic patient with severe mitral regurgitation and an ejection fraction of 0.55.
- C. An asymptomatic patient with mitral stenosis and a pulmonary artery pressure of 60 mm Hg.
- D. An asymptomatic patient with an Austin Flint murmur and an ejection fraction that has decreased from 0.60 to 0.45.
- E. A patient with functional mitral regurgitation, class II symptoms, and a left bundle branch block.

Answer: E A patient with functional mitral regurgitation should undergo evaluation for cardiac resynchronization therapy, which might substantially improve his or her mitral regurgitation. A patient with aortic stenosis has classic symptoms that require aortic valve replacement. Pulmonary hypertension in mitral stenosis worsens prognosis, so further delay is contraindicated. The other two patients have developed left ventricular dysfunction requiring prompt surgical intervention to prevent further deterioration.

4. The best defined need for medical therapy in valve disease is

- A. the use of vasodilators in chronic aortic regurgitation.
- B. the use of statins in aortic stenosis.
- C. the use of vasodilators in asymptomatic aortic regurgitation.
- D. the use of vasodilators in asymptomatic mitral regurgitation.
- E. the use of warfarin in patients with mitral stenosis, atrial fibrillation, and a remote history of peptic ulcer disease.

Answer: E The risk of stroke in the patient with mitral stenosis far outweighs the small risk of gastrointestinal bleeding. Statins in aortic stenosis and vasodilators in asymptomatic regurgitant disease have not been proven to be effective.

5. The least desirable option for the treatment of severe valvular heart disease is

- A. mitral repair for mitral regurgitation.
- B. balloon valvotomy for mitral stenosis.
- C. mitral valve replacement for a patient with posterior leaflet prolapse.
- D. a pulmonary autograft for a young patient with aortic stenosis.
- E. a tricuspid valve repair for tricuspid regurgitation.

Answer: C Mitral valve replacement for a patient with simple posterior leaflet prolapse that can easily be repaired is an error in management because mitral valve repair is far superior to mitral valve replacement. Balloon valvotomy is preferred over surgery in most cases of mitral stenosis. A pulmonary autograft is a good choice in a young patient in whom lifelong anticoagulation with a mechanical valve may be undesirable.

Ch / 76 INFECTIVE ENDOCARDITIS

1. A 76-year-old man with known rheumatic valvular heart disease underwent elective mitral valve replacement with a Saint Jude prosthetic valve. His dentist calls you for advice regarding choice of antibiotic prophylaxis before dental extraction because the patient had developed bronchospasm and a diffuse urticarial rash after amoxicillin administration before a dental cleaning approximately 6 months ago. Which antibiotic should be administered?

- A. Clindamycin 600 mg orally 1 hour before the procedure
- B. Cefuroxime axetil 500 mg orally before the procedure
- C. Amoxicillin 2 g intravenously 1 hour before the procedure with corticosteroid and antihistamine coverage
- D. Nafcillin sodium 2 g IV 1 hour before the procedure
- E. Gentamicin sulfate 1 mg/kg IV 1 hour before the procedure

Answer: A The current (2007) AHA guidelines recommend clindamycin in patients who have a history of an immediate type hypersensitivity reaction to β -lactam antibiotics, which this patient demonstrated. Therefore, amoxicillin, cephalosporins, and nafcillin should be avoided. Levofloxacin and gentamicin are not recommended in these guidelines. (Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. 2007;116:1736-1754.)

2. A 68-year-old man with diabetes on chronic hemodialysis developed the acute onset of fever, chills, and left-sided abdominal pain. He had an ICD implanted 3 years ago. Blood cultures grew *Staphylococcus aureus*, and transesophageal echocardiography demonstrated vegetations on the mitral valve. Splenic infarctions were seen on computed tomographic scanning. Which one of the following is *true* regarding this presentation?

- A. Health care–associated infection is accounting for an increasing number of infective endocarditis cases in this country.
- B. *Escherichia coli* is a common cause of infective endocarditis in the hemodialysis population.
- C. Pending susceptibility testing results, gentamicin should be administered.
- D. To reduce health care costs, transthoracic echocardiography should have been performed instead of transesophageal echocardiography.
- E. For chronic hemodialysis, a tunneled catheter has a lower risk of blood stream infection compared with an arteriovenous fistula.

Answer: A Health care exposure accounts for an increasing number of cases of infective endocarditis in developed countries. *Staphylococcus aureus*, including methicillin-resistant strains, is a common cause of these infections. Empiric vancomycin should be administered until susceptibility results are known. (Athan E, Chu VH, Tattavin P, et al. Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices. *JAMA*. 2012;307:1727-1735.)

3. A 55-year-old veterinarian presents with several months of low-grade fever and night sweats. On an echocardiograph, he has evidence of endocarditis. Despite no recent antibiotic therapy, three sets of blood cultures remain negative for 7 days. Which one of the following is the most likely pathogen?

- A. Coagulase-negative staphylococcus
- B. *Coxiella burnetii*
- C. *Enterococcus faecium*
- D. *Escherichia coli*
- E. Orf virus

Answer: B Exposure to animals, particularly sheep and goats, is a risk factor for *Coxiella* infection and a well-known cause of culture-negative endocarditis. Orf virus does not cause endocarditis. The other choices should result in positive blood culture results in a patient who has infective endocarditis and who has not received antibiotic therapy recently. (Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation*. 2005;111:e394-434.)

4. A 78-year-old woman presents with left upper chest pain, swelling, and purulent drainage at the site where a permanent pacemaker generator was implanted. She has had no fever or chills, and her white blood cell count is normal. She underwent generator exchange 4 months ago and underwent a dental cleaning without prophylaxis 3 months ago. Which one of the following is *true* regarding cardiac implantable electronic device (CIED) infections?

- A. Surgical site prophylaxis has not been shown to reduce the risk of a CIED site infection.
- B. Prophylactic antibiotic should have been given before her dental cleaning.
- C. Device manipulation is a risk factor for device infection.
- D. The most likely cause of this infection is a HACEK organism.
- E. Antibiotic therapy for 4 weeks will likely cure the device infection without the device being removed.

Answer: C Manipulation of an implantable cardiac device is associated with the development of acute infection. Antibiotic prophylaxis before manipulation of the surgical site is beneficial, but dental prophylaxis is not. The most likely cause is *Staphylococcus* spp., and removal of the device is required for cure of the infection. (Baddour LM, Cha YM, Wilson WR. Clinical practice. Infections of cardiovascular implantable electronic devices. *N Engl J Med*. 2012;367:842-849.)

5. A 25-year-old morbidly obese man who injects heroin and cocaine presents with fever and blood cultures that grow *Staphylococcus aureus*. He had a past history of prior *S. aureus* blood stream infection 2 years ago, when he had an allergic reaction to vancomycin. At that time, he had evidence of tricuspid valve endocarditis. Which one of the following is *true*?

- A. A transthoracic echocardiography should be obtained.
- B. Initial empiric therapy should include daptomycin until susceptibility results are known.
- C. His mortality risk is high (>50%).
- D. Two weeks of antibiotic therapy should be curative.
- E. Rifampin should be administered.

Answer: B Daptomycin should be administered in case the blood culture isolate is methicillin-resistant *Staphylococcus aureus*. Transesophageal, rather than transthoracic, echocardiography should be obtained to evaluate for both right-sided and left-sided endocarditis. Cure rates with active antibiotic therapy for 2 weeks are high, provided there is no evidence of left-sided endocarditis or of metastatic foci of infection. Rifampin is not routinely recommended in native valve infections caused by staphylococci. (Fowler VG Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med*. 2006;355:653-665.)

1. With the following pressures, calculate the patient's ankle-brachial index: right arm, 150/80 mm Hg; left arm 120/98 mm Hg; right dorsalis pedis, 100/50 mm Hg; right posterior tibial, 60/40 mm Hg; left dorsalis pedis, 75/50 mm Hg; and left posterior tibial, 40/20 mm Hg.

- A. Right, 0.66; left, 0.50
- B. Right, 0.50; left, 0.33
- C. Right, 0.40; left, 0.33
- D. Right, 0.66; left, 0.625

Answer: A The highest arm systolic pressure is used as the denominator (150 mm Hg) with the highest ankle systolic pressure on the right (100 mm Hg) and left (75 mm Hg) as the numerator.

2. Which of the following has the strongest effect on late patency for femoropopliteal stents?

- A. Stent type: stainless steel vs. nitinol.
- B. Stent length: ≤ 7 cm vs. longer.
- C. Lesion length: ≤ 7 cm vs. longer.
- D. Multiple vs. single stents placed.

Answer: C Lesion length is the strongest predictor of long-term stent patency in the femoropopliteal artery.

3. Which new technology holds the most promise for improving femoropopliteal artery endovascular results?

- A. Laser angioplasty
- B. Drug-eluting stents
- C. Directional atherectomy
- D. Cryoplasty

Answer: B Randomized trial evidence documents the improved outcomes with drug-eluting stents compared with primary angioplasty or provisional bare metal stents. Laser angioplasty, atherectomy, and cryoplasty have not demonstrated improved outcomes compared with conventional therapy.

4. Which of the following serious complications is most likely to occur with magnetic resonance angiography imaging of the lower extremities?

- A. Contrast-induced nephropathy
- B. Anaphylaxis to gadolinium contrast
- C. Nephrogenic systemic fibrosis
- D. Hemolytic anemia

Answer: C The major toxicity of gadolinium is an uncommon but potentially lethal systemic disorder called nephrogenic systemic fibrosis or nephrogenic sclerosing dermopathy (Chapter 267). A glomerular filtration rate of 60 mL/min or less is the major risk factor.

5. The major advantage for magnetic resonance angiography (MRA) over computed tomography angiography (CTA) for lower extremity imaging is

- A. lower total diagnostic costs.
- B. better imaging of calcified arteries.
- C. better imaging of metallic stents.
- D. more rapid imaging.

Answer: B Calcifications can cause artifacts that may be misdiagnosed as stenosis in CTA but not magnetic resonance angiography. An advantage of computed tomographic angiography over MRA is its ability to visualize metallic stents and stent grafts (see Fig. 79-4). CTA can be performed more quickly and with less pretreatment planning than MRA. In a randomized trial comparing MRA with CTA for initial imaging in peripheral arterial disease, there was no difference between the two techniques in terms of ease of use, clinical utility, or patient outcome, but CTA reduced total diagnostic costs.

Ch / 80 OTHER PERIPHERAL ARTERIAL DISEASES

1. Suspicion of popliteal artery entrapment syndrome should occur in which of the following?

- A. A 66-year-old woman with hypertension, tobacco use, and exertional limb discomfort
- B. A 27-year-old tobacco-using man with ischemic rest pain of the right third digit and superficial thrombophlebitis
- C. A 52-year-old with red discoloration of the feet with heat exposure
- D. A 22-year-old male athlete who has bilateral calf claudication with long-distance cycling
- E. A 31-year-old woman with hypertension and right femoral artery bruit

Answer: D Popliteal artery entrapment should be considered as a cause of intermittent claudication in young patients without evidence of atherosclerosis or other systemic inflammatory disorders.

2. Fibromuscular dysplasia is classically represented by which of the following?

- A. Arterial calcification and stenosis
- B. New-onset hypertension and a cervical bruit in a healthy 34-year-old woman
- C. Cyanosis with ischemic rest pain of the toes
- D. A rapidly expanding ascending thoracic aortic aneurysm
- E. Carotid artery dissection in a 61-year-old man after a motor vehicle accident

Answer: B Fibromuscular dysplasia is often found incidentally in patients undergoing imaging tests for other reasons. Patients are more commonly younger and female, with the most common finding being hypertension.

3. The most common clinical manifestations of erythromelalgia include which of the following?

- A. Presentation in late fall or early winter
- B. Intense itching in the hands and feet
- C. Increased warmth, erythema, and a burning sensation in the feet
- D. History of trauma as the inciting event
- E. Little effect on patient's quality of life

Answer: C Erythromelalgia is a cold-induced vascular disorder that predominantly causes erythema, heat, and burning in the feet.

4. What are the most common clinical characteristics of pernio?

- A. Intense itching and burning pain, more commonly seen in females
- B. Edema and burning pain that is exacerbated by warmer temperatures
- C. May result in amputation if not recognized
- D. Stasis ulceration is common
- E. Anticoagulation is the treatment of choice

Answer: A Pernio, also known as chilblains, is a cold-induced vascular disorder characterized by seasonal itching, burning, and discoloration of the toes, more often in women than men. It does not routinely ulcerate, does not result in amputation, and requires only aggressive thermal protection during the winter months.

1. Which of the following statements about D-dimer testing is true?

- A. When abnormal, the test is diagnostic of VTE.
- B. The test can be used to diagnose pulmonary embolism when the pretest probability is high or intermediate.
- C. When the results are normal in combination with a low pretest probability in suspected DVT, DVT can be excluded.
- D. The degree of elevation accurately estimates clot size.
- E. All of the above.

Answer: C D-Dimer is a sensitive but not specific test for diagnosing VTE. As a result, a negative test in a low-risk patient effectively excludes the diagnosis.

2. Which of the statements about VTE in pregnancy is untrue?

- A. In at least 80% of pregnant women with DVT, the left leg is involved.
- B. Warfarin is contraindicated in pregnant women between 6 and 12 weeks of gestation because of the potential to cause warfarin embryopathy.
- C. When bleeding occurs at injection sites of LMWH, it is worthwhile to review the injection technique and to check the hemoglobin, hematocrit, platelet count, and anti-factor Xa level.
- D. When heparin-induced thrombocytopenia is suspected in pregnant women treated with unfractionated heparin, LMWH is a reasonable substitute because there is minimal cross-reactivity of the causative antibody with LMWH.
- E. None of the above.

Answer: D LMWH frequently cross-reacts with the heparin-induced thrombocytopenia antibody and can perpetuate the associated thrombotic complications.

3. Which of these statements about post-thrombotic syndrome is incorrect?

- A. It inevitably leads to skin ulcers.
- B. There is no gold standard test to diagnose it.
- C. There is some doubt about whether elastic stockings prevent it.
- D. It can be confused with recurrent DVT.
- E. None of the above.

Answer: A Only a small proportion of subjects who develop post-thrombotic syndrome will progress to develop skin ulcers.

1. Which of the following is true about cough variant asthma?

- A. The diagnosis requires an improvement in the cough with traditional asthma medications.
- B. It does not reverse with a bronchodilator.
- C. Sputum eosinophils are absent.
- D. The cough is not responsive to inhaled corticosteroids.
- E. Hemoptysis has been present on two occasions.

Answer: A Cough variant asthma responds to asthma medications, in contrast to other causes of cough, which may be either partially or not affected by traditional asthma medications.

2. A 53-year-old woman returns for reevaluation of cough of 1 year duration. The cough is occasionally productive, occurs during the day and night, and is triggered by talking, laughing, and cold air. Her pulmonary function tests are normal. The cough has not responded to appropriate therapy for asthma with inhaled corticosteroids and short-acting β -agonists. She denies any history of lung disease, cigarette smoking, atopy, rhinitis, gastroesophageal reflux disease, or obstructive sleep apnea. The physical examination is unrevealing. Further evaluation, including esophageal impedance and manometry, were unremarkable. What is the appropriate next step in this patient's management?

- A. High-resolution computed tomography of the chest
- B. Computed tomography of the sinuses
- C. Bronchoscopy
- D. Echocardiogram
- E. Video laryngeal swallowing study

Answer: A With a cough that is productive, even occasionally, an assessment of airway structure via computed tomography should be performed first before bronchoscopy to assess for bronchiectasis, sarcoidosis, or occult interstitial lung disease. The patient has no history of atopy or rhinitis, so sinus computed tomography is not indicated. A cough due to cardiac causes is less likely to be productive, so an echocardiogram is not indicated. The likely diagnosis is mild bronchiectasis causing cough.

3. A 55-year-old man presents with dyspnea on exertion beginning approximately 2 months ago. He denies chest pain, cough, wheezing, chest tightness, or a history of cardiovascular disease, lung disease, diabetes, or cigarette smoking. He takes medication daily for hypertension and gastroesophageal reflux disease. He does not exercise regularly. His BMI is 36 kg/m². On physical examination his blood pressure is 135/70, and his other vital signs and examination are normal. Pulmonary function tests, chest radiograph, complete blood count, and brain natriuretic peptide levels are normal. What is the next appropriate step in this patient's evaluation?

- A. Echocardiogram
- B. Pulse oximetry with ambulation (6-minute walk test)
- C. Exercise treadmill test
- D. High-resolution chest computed tomography
- E. 24-hour Holter monitoring

Answer: C This patient likely has coronary artery disease manifesting as dyspnea on exertion. His risk factors include hypertension, obesity, and lack of exercise. With a normal chest radiograph and pulmonary function tests, primary lung diseases are less likely. A normal brain natriuretic peptide level makes reduced cardiac function less likely, and anemia is excluded by a normal complete blood count. Cardiovascular disease is the most likely diagnosis, and additional testing likely will be required if the exercise treadmill test is unrevealing.

4. A 40-year-old woman with a history of atopy, rhinitis, and gastroesophageal reflux disease (GERD) presents with wheezing of 3 months duration. The wheezing occurs primarily during the day, is triggered by cold air and exercise, and has not responded to a 6-week course of an inhaled corticosteroid and short-acting β -agonist. She denies chest tightness, chest pain, or a history of lung or cardiovascular disease. Her history is notable for allergies to dust, multiple weeds, grasses, and animal dander. She has persistent rhinitis for which she performs nasal saline rinses and uses intranasal corticosteroids daily. She also takes a proton pump inhibitor once daily for treatment of GERD, and these symptoms are well controlled. Her physical examination reveals normal vital signs and erythema of the upper airway without nasal polyps. The remainder of her physical examination is normal without wheezing. Pulmonary function tests, chest radiograph, brain natriuretic peptide, and methacholine challenge testing are normal. What is the next step in this patient's evaluation?

- A. Sinus computed tomography
- B. High-resolution chest computed tomography
- C. Direct laryngoscopy after exercise
- D. Echocardiogram
- E. Bronchoscopy with biopsy

Answer: C This presentation suggests vocal cord dysfunction presenting as wheezing. Wheezing in the setting of rhinitis and GERD suggests an airway process as the most likely diagnosis. Because the patient has not responded to therapy for asthma and a methacholine challenge is negative, asthma is highly unlikely. A normal BNP makes cardiac dysfunction less likely. In the setting of rhinitis and GERD, evaluation of the upper airway to exclude vocal cord dysfunction during an episode of wheezing is the next appropriate step. An echocardiogram should be obtained if direct laryngoscopy is negative.

1. Concerning chest radiography, which of the following statements is incorrect?

- A. Chest radiography is the most commonly performed imaging procedure.
- B. Chest radiography provides useful information at modest monetary cost with very low radiation exposure.
- C. Chest radiographs were previously obtained by digital imaging but are preferentially performed with cassettes and radiographic film.
- D. The standard chest radiograph is performed in frontal and lateral projections.
- E. The chest radiographs should be obtained at total lung capacity.

Answer: C Chest radiographs were previously obtained with film and cassette and now are acquired digitally.

2. Concerning the radiologic distinction between alveolar and interstitial patterns, which of the following statements is incorrect?

- A. Correlation between radiographic localization to an anatomic compartment and the actual histopathologic finding is poor.
- B. Nodular patterns can be seen in either interstitial or alveolar disease.
- C. Alveolar diseases can induce an interstitial reaction.
- D. Air-bronchograms are seen only in airspace disease.
- E. Ground-glass opacities can be induced by either interstitial or alveolar disease.

Answer: D Air bronchograms are visualized whenever the lung parenchyma, including the alveolar and interstitial compartments that surround gas-containing bronchi, becomes opacified. The resulting contrast between soft tissues and gas yields the air-bronchograms.

3. The size of pleural effusions can be estimated as noted below, except:

- A. The minimum visible on a lateral decubitus examination is 200 mL.
- B. On a lateral chest radiograph, 75 mL can be identified.
- C. On the frontal chest radiograph, 120 mL can be identified.
- D. Five hundred milliliters obscures the ipsilateral hemidiaphragm.
- E. Up to 1000 mL are present if the meniscoid arc reaches the level of the fourth anterior rib.

Answer: A The smallest amount of pleural effusion visible on decubitus radiographs is 10 mL.

1. Which of the following is currently the treatment of choice for Cheyne- Stokes breathing in congestive heart failure?

- A. Optimize medical therapy
- B. Nasal continuous positive airway pressure
- C. Nasal bilevel positive airway pressure
- D. Oral appliance therapy
- E. Uvulopalatopharyngoplasty

Answer: A The treatment of choice for Cheyne-Stokes breathing is currently optimization of medical therapy for the underlying heart failure. Trials of nasal continuous positive airway pressure have failed to improve outcome compared with usual care. Bilevel therapy has not been rigorously studied but may make the situation worse. Although the upper airway can sometimes narrow or collapse in central apnea, there is no role for oral appliance therapy or uvulopalatopharyngoplasty in the absence of obstructive sleep apnea.

2. Which of the following best defines the measurement of loop gain in control of breathing?

- A. A measure of cardiac output
- B. A measure of extravascular lung fluid
- C. A measure of hemoglobin concentration
- D. A measure of the tendency toward instability in the ventilatory control system
- E. A measure of partial pressure of oxygen in the arterial circulation

Answer: D Loop gain refers to the overall instability in a negative feedback control system, such as the ventilatory control system, whose role is to maintain P_{aCO_2} levels. The other factors listed can all influence control of breathing in some way but are not defining loop gain.

3. Which of the following is the gene associated with the central congenital hypoventilation syndrome?

- A. *CFTR*
- B. *PHOX2B*
- C. *A1AT*
- D. *RET*
- E. *BMP*

Answer: B The *PHOX2B* gene is the hallmark for the diagnosis of central congenital hypoventilation syndrome. The other genes have been associated with various respiratory conditions but not with the central congenital hypoventilation syndrome.

4. Which of the following is true regarding obesity-hypoventilation syndrome?

- A. Serum bicarbonate is a useful screening test.
- B. Leptin deficiency is generally seen in afflicted humans.
- C. Obstructive sleep apnea is uncommon in afflicted patients.
- D. It is present in roughly 50% of patients with obstructive sleep apnea.
- E. Hypercapnia usually persists despite major weight loss.

Answer: A Serum bicarbonate is a useful screening test because it is elevated in the majority of patients with chronic hypoventilation. Leptin is deficient in some animal models but rare in human obesity. Obstructive sleep apnea is common in the obesity-hypoventilation syndrome, and obesity-hypoventilation syndrome is seen in roughly 10% of obstructive sleep apnea. Weight loss usually improves gas exchange in these patients.

5. Which of the following is true regarding sleep stages in sleep apnea?

- A. Obstructive sleep apnea is generally worst during slow wave sleep.
- B. Cheyne-Stokes breathing is generally worst during REM sleep.
- C. Periodic breathing at altitude usually resolves during REM sleep.
- D. Obstructive sleep apnea is rare during REM sleep.
- E. Arousal in obstructive sleep apnea has no major effect on breathing.

Answer: C Both Cheyne-Stokes and periodic breathing at altitude are improved in REM compared with NREM sleep. Slow wave sleep is associated with improvement in obstructive sleep apnea. Arousal in obstructive sleep apnea can serve to restore pharyngeal airway patency and allow the resumption of effective tidal breathing.

Ch / 87 ASTHMA

1. A 25-year-old woman who works in an office complains of shortness of breath during the recovery period from her usual aerobic exercise routine. She had a history of asthma as a child, but it went into remission when she was in junior high school. What single test would be the best to order to easily confirm that she is now having a return of her asthma?

- A. Blood eosinophils
- B. Measurement of forced vital capacity before and after bronchodilator
- C. Measurement of the forced expiratory volume in the first second (FEV1) before and after bronchodilator
- D. Testing for airway hyperresponsiveness with inhalation of cold air
- E. Measurement of the diffusion capacity for carbon monoxide

Answer: C If the FEV1, measured before and after bronchodilator treatment, shows an improvement of 12% or more (assuming an absolute increase in the FEV1 of at least 200 mL), this finding would be diagnostic of asthma in this setting. The same is not true of the forced vital capacity. Measurement of airway hyperresponsiveness would make the diagnosis but is complicated and time-consuming. Measurements of blood eosinophils or diffusion capacity are not indicated in this setting.

2. For the same patient as in question 1, you take a medical history to determine if her asthma is in control. Which of the following questions would you *not* need to ask?

- A. Has she been able to sleep through the night without asthma symptoms?
- B. How often has she needed to use her rescue inhaler to control her asthma symptoms?
- C. Has she needed to seek unscheduled medical care for her asthma?
- D. Can she fulfill the activities of her daily life without asthma symptoms?
- E. Is she able to scuba dive without difficulty?

Answer: E Answers A through D are part of the information that should be sought from all asthma patients. Patients with asthma should not scuba dive.

3. A 35-year-old woman with asthma comes for her yearly checkup. For the past year, she has been treated with an albuterol inhaler that she uses on an as-needed basis. During this time, she has used two inhalers (each with 200 puffs of treatment) and no other asthma medications. She is able to sleep through the night without asthmatic symptoms. She is able to participate in all her desired activities, including a regular exercise routine, without asthmatic symptoms, except during the colder months of the year, when she pretreats herself with albuterol before running. She has not had any unscheduled visits for asthma care. Her lung function test results are essentially normal. At this point you should

- A. Add an inhaled corticosteroid at low dose to her asthma regimen
- B. Add a leukotriene modifier to her asthma regimen
- C. Add a combination inhaler (long-acting β -agonist and inhaled corticosteroid)

- D. Leave her regimen as it is
- E. Remove her albuterol before she becomes addicted to it

Answer: D She is well controlled while she is treated with albuterol alone. There is no need to add or to subtract other therapies.

4. A 25-year-old woman whose asthma is in good control comes to your office indicating that she and her husband are trying to have a child. Her only treatment has been inhaled albuterol on an as-needed basis, and she uses about four inhalers (each contains 200 puffs of medication) a year. What is the single statement most likely to be true about her asthma treatment?

- A. There is no need to change her treatment while she is trying to conceive or becomes pregnant.
- B. She should stop the albuterol inhaler and simply “suffer through” any asthma events.
- C. She should continue the albuterol inhaler and start an inhaled corticosteroid.
- D. She should consult an asthma specialist now before she attempts to become pregnant.
- E. She should begin to use her albuterol inhaler on a regularly scheduled basis, two puffs four times a day.

Answer: A There is no need to change her asthma therapy at this time because albuterol is safe to use during pregnancy. The other answers are, by elimination, incorrect.

Ch / 88 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

1. A 54-year-old man seeks medical attention because of increasing exercise intolerance. He works as a construction worker and finds it increasingly difficult to complete the assigned work. He started smoking at the age of 18 years and currently smokes about one pack per day. In addition to dyspnea, he also has daily cough and sputum and admits to frequent “chest colds.” A diagnosis of COPD is strongly suspected. Which of the following would constitute the most appropriate initial assessment?

- A. History and physical examination; spirometry; chest computed tomography; oximetry
- B. History and physical examination; spirometry; electrocardiogram; oximetry
- C. History and physical examination; spirometry; diffusing capacity for carbon monoxide; arterial blood gases
- D. History and physical examination; spirometry; chest radiograph; oximetry
- E. History and physical examination; lung volumes; chest radiograph; arterial blood gases

Answer: D On the basis of the history, a diagnosis of COPD is likely in this patient. Clinical suspicion must always be confirmed by spirometry to demonstrate airflow obstruction and, if it is present, to obtain information about severity. Measurements of lung volumes or the diffusing capacity for carbon monoxide are more complex than spirometry and provide little additional clinically useful information. Chest computed tomography is superior to a chest radiograph in defining the presence and severity of emphysema, but this information presently has no practical implications for managing most COPD patients. Assessment of need for supplemental oxygen can be done with oximetry or arterial blood gases. For patients with stable disease, oximetry is preferred because it is simple and noninvasive.

2. A 63-year-old woman with severe COPD confirmed by spirometry (FEV₁/FVC, 0.53; FEV₁, 37% of predicted) was admitted to the hospital with an exacerbation. At time of discharge, her arterial oxygen saturation was 81% while breathing ambient air at rest. She was given a prescription for home oxygen. At a follow-up visit 3 months later, the patient stated that she had fully recovered from the exacerbation and was able to resume all of her usual activities. Her arterial oxygen saturation at this time was 86%, again while breathing ambient air at rest. Which of the following is the most appropriate recommendation?

- A. Discontinue home oxygen as the patient has fully recovered clinically

- B. Continue oxygen long term, titrate oxygen flow rate to ensure an arterial oxygen saturation of 90% or higher, and instruct the patient to use oxygen at least 18 hours daily
- C. Continue home oxygen with instructions that it be used only if the patient feels more breathless
- D. Use oxygen only during sleep and with exercise
- E. Prescribe oxygen at a flow rate of 2 L/min with instructions to use it at least 12 hours daily

Answer: B This patient has severe COPD with persistent hypoxemia after recovery from a severe exacerbation. Long-term oxygen should be prescribed because it improves all-cause mortality in such patients, and 18 hours of daily use is better than 12 hours. Long-term oxygen may confer other benefits, such as improved neurocognitive function and reduced risk of pulmonary hypertension. When long-term oxygen is first prescribed, the flow rate should be titrated to achieve an arterial oxygen saturation of at least 90%. In patients who do not qualify for long-term oxygen but experience modest desaturation with exercise, oxygen therapy has not been shown to decrease breathlessness or to increase daily activity.

3. A 68-year-old man with long-standing, severe COPD presents to an emergency department with a several-day history of increasing breathlessness, coupled with worsening cough and purulent sputum. After a brief evaluation, it is determined that hospitalization is required. The admitting physician obtains a history and physical examination, which reveals a severely breathless patient with audible expiratory wheezing. A chest radiograph shows hyperinflation and a focal pneumonic infiltrate. An electrocardiogram is unremarkable except for a sinus tachycardia. Routine laboratory test results are normal, and arterial blood gas analysis on ambient air shows a Po₂ of 48 mm Hg, a Pco₂ of 64 mm Hg, and a pH of 7.18. The patient is capable of swallowing oral medications. Which of the following would constitute the most appropriate treatment?

- A. Respiratory antibiotic appropriate to the locale; prednisone given orally (40 mg daily for 5 days); short-acting bronchodilator by nebulizer every 4 to 6 hours; supplemental oxygen sufficient to raise saturation to 90%; noninvasive positive-pressure ventilation
- B. Respiratory antibiotic appropriate to the locale; prednisone given orally (40 mg daily for 5 days); short-acting bronchodilator by nebulizer every 4 to 6 hours; supplemental oxygen sufficient to raise saturation to 90%; intubation and mechanical ventilation
- C. Respiratory antibiotic appropriate to the locale; prednisone given orally (40 mg daily for 5 days); short-acting bronchodilator by nebulizer every 4 to 6 hours; intravenous theophylline; supplemental oxygen sufficient to raise saturation to 90%; noninvasive positive-pressure ventilation
- D. Respiratory antibiotic pending results of sputum culture; prednisone given orally (40 mg daily for 5 days); short-acting bronchodilator by nebulizer every 4 to 6 hours; supplemental oxygen sufficient to raise saturation to 90%; noninvasive positive-pressure ventilation
- E. Respiratory antibiotic appropriate to the locale; methylprednisolone given intravenously (30 mg four times daily for 10 days); short-acting bronchodilator by nebulizer every 4 to 6 hours; supplemental oxygen sufficient to raise saturation to 90%; intubation and mechanical ventilation

Answer: A Although never tested in rigorous randomized clinical trials, there is a consensus that regularly scheduled short-acting bronchodilators and controlled supplemental oxygen are beneficial for hospitalized patients with COPD. Antibiotics appear to be most beneficial for COPD exacerbations that result in hospitalization. No single antibiotic is proven to be superior to any other, and the choice should be based primarily on local bacterial resistance patterns. There is very good evidence that systemic corticosteroids improve clinical outcomes in this setting as well as good evidence that short courses of oral prednisone are as effective as longer courses. Several small, randomized clinical trials failed to show any benefit from theophylline in hospitalized COPD patients, and gastrointestinal side effects can be troublesome. Strong evidence supports the use of noninvasive positive-pressure ventilation, rather than intubation and mechanical ventilation, for COPD patients with mild to moderate respiratory failure.

4. A 53-year-old woman with severe COPD confirmed by spirometry is seen in the office because of progressive dyspnea with exertion to the point that she could walk only one block on the level before having to stop and catch her breath. She has regularly smoked cigarettes continuously since she was 18 years old and still smokes half a pack per day. She made two visits to emergency departments in the previous year for "bronchitis," and on each visit she had been given an antibiotic but no other respiratory medications. She has no known history of cardiac disease. Examination of the chest reveals signs of lung hyperinflation with decreased breath sounds. The chest radiograph shows signs of hyperinflation. Spirometry results include an FEV1/FVC of 0.53 and an FEV1 of 37% of predicted, thus confirming the diagnosis of severe COPD. Oxygen saturation at rest on ambient air is 90%. Which of the following would constitute the most appropriate management plan for this woman with newly diagnosed severe, exacerbation-prone COPD?

- A. Smoking cessation; short-acting bronchodilator; long-acting β_2 -adrenergic bronchodilator or long-acting anticholinergic bronchodilator
- B. Smoking cessation; short-acting bronchodilator; long-acting β_2 -adrenergic or long-acting anticholinergic bronchodilator; theophylline; pulmonary rehabilitation
- C. Smoking cessation; short-acting bronchodilator; combination inhaled therapy with a long-acting β_2 -adrenergic bronchodilator, a long-acting anticholinergic bronchodilator, or a glucocorticosteroid; low-dose prednisone (10-15 mg daily)
- D. Smoking cessation; short-acting bronchodilator; combination inhaled therapy with at least two of the following: long-acting β_2 -adrenergic bronchodilator, long-acting anticholinergic bronchodilator, inhaled glucocorticosteroid; pulmonary rehabilitation
- E. Smoking cessation; short-acting bronchodilator; long-acting β_2 -adrenergic or anticholinergic bronchodilator; daily azithromycin; ambulatory oxygen

Answer: D This woman with newly diagnosed COPD has severe airflow obstruction by spirometric criteria, a pronounced limitation of exercise, and a history of two exacerbations in the past year. Smoking cessation is the most important element in her long-term care. The severity of her disease would justify combination therapy including at least two of these three classes of inhaled drugs: long-acting β_2 -adrenergic bronchodilators, long-acting anticholinergic bronchodilators, or inhaled glucocorticosteroids. Theophylline and daily azithromycin are not considered first-line treatment of COPD. Chronic prednisone is not known to be clinically effective in patients with stable COPD but is known to cause harm. Assuming that the patient is motivated and that a program is available, pulmonary rehabilitation is recommended for all patients who have exercise-limiting COPD.

5. A 58-year-old woman with severe COPD has become increasingly incapacitated from her lung disease to the point that she is able to walk only about a half-block. She was once very physically active but has had to curtail most of these activities. She is compliant with her medications (including an inhaled short-acting bronchodilator, an inhaled long-acting bronchodilator, an inhaled corticosteroid, and theophylline), but she finds that these medications have had only modest effect on her exercise tolerance. She quit smoking 10 years ago and has no comorbid conditions that should significantly limit her physical activities. Her arterial oxygen saturation is 92% while at rest and breathing ambient air, but it decreases to 86% after a brisk walk down the hallway. Which of the following is the most appropriate intervention at this stage of the disease?

- A. Ambulatory oxygen
- B. Lung volume reduction surgery
- C. Lung transplantation
- D. A pulmonary vasodilating drug
- E. Pulmonary rehabilitation

Answer: E Assuming that the patient is motivated, has no other severe disabling comorbid conditions, and has access to a program, pulmonary rehabilitation has been shown to increase walking distance and respiratory health status substantially. Most rehabilitation programs are only 6 to 12 weeks in length, and the clinical benefits that accrue during that period erode during the ensuing year unless a longer-term program is put in place. Lung volume reduction surgery or a lung transplant may be

considered at a later stage of her disease if all other interventions fail. The best available evidence raises serious doubts that ambulatory oxygen confers significant clinical benefits when it is prescribed for isolated exercise-induced hypoxemia. Studies of limited size have failed to show that pulmonary vasodilators are of any clinical benefit in COPD.

Ch / 89 CYSTIC FIBROSIS

1. A 27-year-old male with a nagging, productive cough is known to be infertile. Which diagnostic approach is NOT likely to be helpful in determining whether he has cystic fibrosis?

- A. Ultrasonography of the kidneys
- B. Sweat test
- C. Extended CFTR genotype analysis
- D. Sputum culture
- E. Exploration of family history looking for deaths in childhood

Answer: A The kidneys are not usually affected in cystic fibrosis, at least to the extent that can be appreciated on ultrasonography. The other tests can all reveal supportive evidence of the diagnosis of cystic fibrosis.

2. Considering the same 27-year-old man as in question 1, the sweat test result comes back abnormal at 78 mmol/L. Which of the following statements regarding this patient's care is INCORRECT?

- A. You tell him that it is unlikely that he will need follow-up at a cystic fibrosis center because he was diagnosed at such a late age.
- B. You should order a mutation analysis to define his genotype.
- C. You should order lung function testing.
- D. You should order a high-resolution computed tomography scan of his chest looking for bronchiectasis.
- E. You should order a sputum culture.

Answer: A All patients with a diagnosis of cystic fibrosis should have follow-up at a cystic fibrosis care center.

3. Considering the same 27-year-old man as in questions 1 and 2, his lung function testing reveals a forced expiratory volume in 1 second of 65% predicted with no reversibility after a bronchodilator. His computed tomography scan shows definite bronchiectasis. His sputum culture grows *Pseudomonas aeruginosa*. His genotype is G551D/A455E. Which of the following treatments is NOT indicated?

- A. Inhaled tobramycin or inhaled aztreonam daily, one month on and one month off
- B. Inhaled dornase alfa daily
- C. Ivacaftor 150 mg PO twice daily
- D. Oral corticosteroid treatment at 30 mg every other day in the morning.
- E. Daily airway secretion clearance

Answer: D Corticosteroids are not part of the first-time care of cystic fibrosis, and they also can cause complications, especially by making patients more susceptible to infection.

Ch / 90 BRONCHIECTASIS, ATELECTASIS, CYSTS, AND LOCALIZED LUNG DISORDERS

1. Of the following, which organism is associated with the worst prognosis in non-cystic fibrosis bronchiectasis?

- A. *Staphylococcus aureus*
- B. *Escherichia coli*
- C. *Streptococcus pneumoniae*
- D. *Pseudomonas aeruginosa*
- E. *Moraxella catarrhalis*

Answer: D *Pseudomonas aeruginosa* is the correct answer. Molecular techniques have demonstrated that diverse polymicrobial communities are present in the lungs of patients with bronchiectasis, both when they are clinically stable as well as during exacerbations. The dominant organisms are *P. aeruginosa* and *Haemophilus influenzae*, but anaerobic organisms may also be detected.

2. Of the following, which organism found in your patient with bronchiectasis would raise the suspicion for undiagnosed cystic fibrosis?

- A. *Pseudomonas aeruginosa*
- B. *Staphylococcus aureus*
- C. *Mycobacterium avium* complex
- D. *Streptococcus pneumoniae*
- E. *Acinetobacter baumannii*

Answer: B The presence of *Staphylococcus aureus* raises the suspicion for cystic fibrosis, and further testing to establish or exclude this diagnosis is indicated.

3. Which imaging technique is used to confirm the diagnosis of bronchiectasis?

- A. Routine chest radiography
- B. Noncontrast high-resolution CT scan
- C. CT of the chest with contrast
- D. MRI of thorax
- E. Bronchography

Answer: B High-resolution computed tomography of the chest without the need for contrast is the imaging test of choice for confirming bronchiectasis

4. Which of the following is most predictive of poor prognosis in patients with bronchiectasis?

- A. Chronic infection with *Mycobacterium avium* complex
- B. Total lung capacity less than 70% predicted
- C. Admission to the ICU for respiratory failure
- D. Chronic infection with *Staphylococcus aureus*
- E. Dependence on supplemental oxygen

Answer: C When a patient with bronchiectasis has developed respiratory failure, the long-term prognosis is poor. More than 60% of patients admitted to a medical intensive care unit for bronchiectasis will die during that hospitalization.

1. The correct treatment for patient with pulmonary alveolar proteinosis and hypoxemia is

- A. corticosteroids.
- B. lung transplantation.
- C. plasmapheresis.
- D. whole-lung lavage.
- E. azathioprine.

Answer: D Patients with pulmonary alveolar proteinosis and significant clinical findings, such as dyspnea and hypoxemia, should be treated with whole-lung lavage, which is the current standard therapy.

2. Bronchorrhea is a finding sometimes associated with

- A. diffuse alveolar hemorrhage.
- B. pulmonary alveolar proteinosis.
- C. invasive mucinous adenocarcinoma.
- D. cardiogenic pulmonary edema.
- E. ARDS.

Answer: C Bronchorrhea, which is the production of copious amounts of sputum that is usually clear and sometimes salty tasting, is seen in some cases of invasive mucinous adenocarcinoma.

3. Which of the following is best characterized radiographically as an alveolar filling disorder?

- A. Idiopathic pulmonary fibrosis
- B. Lymphangioleiomyomatosis
- C. Acute interstitial pneumonitis
- D. Lymphocytic interstitial pneumonitis
- E. Langerhans cell histiocytosis

Answer: C Acute interstitial pneumonia is characterized radiographically as an alveolar filling process. The other options have an interstitial pattern on chest imaging.

4. The most common type of pulmonary alveolar proteinosis is

- A. acquired or autoimmune.
- B. congenital
- C. associated with hematologic disease.
- D. associated with metal dust exposure.
- E. associated with respiratory infection.

Answer: A Autoimmune processes account for 90% of adult cases of pulmonary alveolar proteinosis, usually caused by GM-CSF antibodies. It also can be congenital or secondary to dust exposure or hematologic malignancy and is the most common form overall.

5. Plasmapheresis is part of the standard treatment for diffuse alveolar hemorrhage caused by which of the following diseases?

- A. Idiopathic pulmonary hemosiderosis
- B. Goodpasture syndrome
- C. Cocaine inhalation
- D. Autologous bone marrow transplantation
- E. Pneumococcal pneumonia

Answer: B Plasmapheresis along with corticosteroids and cyclophosphamide is part of the standard treatment of diffuse alveolar hemorrhage related to Goodpasture syndrome.

Ch / 92 INTERSTITIAL LUNG DISEASE

1. The diagnosis of idiopathic pulmonary fibrosis is ascertained by
- A. bronchoalveolar lavage (BAL) cellular analyses.
 - B. the mere pattern of usual interstitial pneumonia (UIP) in the surgical lung biopsy.
 - C. the mere pattern of usual interstitial pneumonia (UIP) pattern in HRCT image of the chest.
 - D. exclusion of environmental and other clinical conditions of interstitial lung disease (ILD).
 - E. all of the above.

Answer: D It is imperative to exclude all possible factors known to cause or be associated with ILD and pulmonary fibrosis, including the patient's environment (work and domestic), where the patient spends time, connective tissue diseases, and the use of licit and illicit drugs. The clinical features of idiopathic pulmonary fibrosis, including HRCT findings and histopathologic patterns of usual interstitial pneumonia, are nonspecific. A recent prospective study in one center with experienced ILD experts documented that 43% of patients who were diagnosed with idiopathic pulmonary fibrosis based on current 2011 guidelines turned out to have chronic hypersensitivity pneumonitis.

2. Cigarette smoking is *not* known to be a risk factor for
- A. idiopathic pulmonary fibrosis.
 - B. respiratory bronchiolitis.
 - C. pulmonary Langerhans cell histiocytosis.
 - D. desquamative interstitial pneumonia.
 - E. acute interstitial pneumonia.

Answer: E Acute interstitial pneumonia, which is a rare interstitial pneumonia of unknown etiology, occurs acutely in otherwise healthy adults and rapidly progresses to respiratory failure. The radiologic and histopathologic features are of diffuse alveolar damage, similar to patients with acute respiratory distress syndrome. There are no known risk factors for acute interstitial pneumonia, not even cigarette smoking.

Ch / 93 OCCUPATIONAL LUNG DISEASE

1. Which one of the following statements is *not* correct?
- A. Occupational asthma is defined as the new-onset of asthma caused by work.
 - B. Occupational asthma is defined as asthma that is transiently worsened by exposures at work.
 - C. Irritant-induced asthma is a form of work-related asthma that includes reactive airways dysfunction syndrome as the most definitive subtype.
 - D. Asthma that is worsened but not caused by work is termed work-exacerbated asthma.
 - E. Occupational asthma can be associated with immunoglobulin E (IgE) antibodies to the causative exposure agent

Answer: B Occupational asthma is defined as asthma caused by work. Asthma that is transiently worsened at work is termed work-exacerbated asthma (Tarlo SM, Balmes J, Balkissoon R, et al. Diagnosis and management of work-related asthma: American College of Chest Physicians Consensus Statement. *Chest*. 2008;134:1S-41S.). Occupational asthma can be caused by an IgE-mediated response to a workplace sensitizer, but the exact mechanism is unclear for many chemical causes of occupational asthma. High-level irritant exposures can also cause occupational asthma. See Work-Related Asthma section.

2. A former soldier who had been deployed to Afghanistan on three occasions complains of shortness of breath on exertion. His pulmonary function tests and chest radiograph are normal. Which one of the following work-related diagnoses should be considered and further investigated?

- A. Pulmonary hypertension
- B. Constrictive bronchiolitis
- C. Chronic obstructive pulmonary disease (COPD)
- D. Asbestosis
- E. Irritable larynx syndrome

Answer: B Lung biopsy findings of constrictive bronchiolitis have been reported among military personnel with dyspnea on exertion after return from deployment in Asia, often without significant abnormalities on pulmonary function testing or chest imaging. The probable cause is fumes from burn-pits, desert storms, or other inhaled toxic exposures (Kreiss K. Occupational causes of constrictive bronchiolitis. *Curr Opin Allergy Clin Immunol*. 2013;13:167-172).

3. A 40-year-old man has findings of interstitial pulmonary fibrosis. He has worked in a facility making screens for smart phones. Which of the following tests is *not* likely to be helpful in determining whether his lung disease has resulted from his work?

- A. History of alveolar proteinosis among coworkers
- B. Review of material safety data sheets to determine possible exposure to indium-tin oxide
- C. Blood indium assay
- D. Review of lung biopsy for characteristic changes
- E. Pulmonary function tests

Answer: E Indium-tin oxide has caused alveolar proteinosis and pulmonary fibrosis in a subset of exposed workers. Lung biopsy findings have shown alveolar proteinosis or cholesterol clefts. See Table 93-1. (Cummings KJ, Nakano M, Omae K, et al. Indium lung disease. *Chest*. 2012;141: 1512-1521).

4. A 30-year-old man comes to the emergency department with acute fever, malaise, dry cough, chest tightness, and neutrophilia. The chest radiograph is normal. Which of the following is *not* a cause for an acute febrile syndrome?

- A. Stainless steel welding
- B. Cotton dust
- C. Grain handling
- D. Baking
- E. Polymer fume work

Answer: D The other exposures can all cause an acute febrile illness, typically occurring after several hours of exposure and typically worse early in the work week but improving later in the week. See Table 93-6.

1. Which one of the following is *not* part of the pathophysiologic response to drowning?

- A. Reduced surfactant levels and function
- B. Laryngospasm
- C. Increased Pao₂
- D. Apnea
- E. Metabolic acidosis

Answer: C Aspiration, apnea, and laryngospasm all lead to hypoxemia. See Drowning: Pathobiology.

2. Which one of the following is *not* true regarding acute mountain sickness?

- A. The best treatment for life-threatening symptoms is immediate descent, if possible, combined with supplemental oxygen therapy.
- B. Acetazolamide 125 mg orally twice daily, has been shown to be effective in preventing acute mountain sickness.
- C. If descent is not possible, high-altitude pulmonary edema and high-altitude cerebral edema can be fatal.
- D. Individuals who have previously suffered from acute mountain sickness or other diseases of altitude are protected from further episodes during their next ascent.
- E. The pathophysiology centers on the decreased partial pressure of oxygen at altitudes above 7000 feet, leading to decreased oxygen delivery to tissues.

Answer: D People who have developed acute mountain sickness, high-altitude pulmonary edema, or high-altitude cerebral edema are at significantly increased risk for subsequent episodes, especially during rapid ascents. See Diseases of High Altitude.

3. Which one of the following statements is *not* true about decompression sickness?

- A. The symptoms of decompression sickness are related to exposure to increasing ambient pressures.
- B. Breath holding while ascending from a dive leads to pulmonary barotrauma and potentially arterial gas embolism.
- C. Risk factors for decompression sickness include long duration of dives, repetitive dives, heavy exertion at depth, cold water, and rapid ascent.
- D. Bullous or cystic lung disease is a contraindication to diving.
- E. Recompression therapy with 100% oxygen in a hyperbaric chamber is the standard of care for severe or persistent decompression illness associated with diving.

Answer: A Decompression sickness is caused by decreasing ambient pressures, as the partial pressure of nitrogen decreases and tissues that have been supersaturated with nitrogen during descent begin releasing nitrogen into the surrounding tissues and bloodstream in the form of gas bubbles. These gas bubbles then cause damage either by mechanical compression of tissues or embolization through blood vessels to end organs. See Decompression Illness: Decompression Sickness, Barotrauma, and Arterial Gas Embolism.

4. Which one of the following is *not* an appropriate treatment for cyanide poisoning?

- A. Sodium nitrate, 300 mg IV
- B. At least one treatment with hyperbaric oxygen lasting approximately 2 hours; can be repeated a second time if symptoms persist
- C. Hydroxocobalamin, 5 mg IV
- D. Amyl nitrate gas ampules, one 0.3-mL gas ampule each minute
- E. Sodium thiosulfate, 12.5g IV

Answer: B Hyperbaric oxygen therapy, which is central to treatment of decompression sickness and carbon monoxide poisoning, plays no role in cyanide poisoning. See Smoke Inhalation: Cyanide and Other Gases.

5. Which one of the following is *not* a correct statement regarding transfusion-related acute lung injury (TRALI)?

- A. TRALI is a clinical syndrome that can be indistinguishable from acute lung injury or acute respiratory distress syndrome (ARDS).
- B. All blood products are associated with a similar incidence of TRALI.
- C. The causative antibodies are HLA type I or type II or neutrophil-specific antigen antibodies.
- D. Transfusions from women of increasing parity are associated with an increased risk for developing TRALI.
- E. Symptoms of TRALI (tachypnea, hypoxemia, cyanosis, dyspnea and fever) can develop up to 6 hours after the transfusion of blood products.

Answer: B Different blood products carry different risks for causing TRALI, with pooled products carrying the highest risk. See Transfusion-Related Acute Lung Injury.

Ch / 95 **SARCOIDOSIS**

1. Which of the following environmental exposures has been associated with risk for sarcoidosis?

- A. Mold or mildew
- B. Musty odor at work
- C. Agricultural employment
- D. Pesticide using industries
- E. All of the above

Answer: E Several environmental exposures are modestly associated with the risk for sarcoidosis, each with odds ratios of about 1.5: mold or mildew, musty odor at work, agricultural employment, and pesticide-using industries. Highly sensitive methods for detecting microbial DNA and proteins, such as polymerase chain reaction and mass spectrometry, have yielded potential etiologic agents. One promising candidate of microbial origin is the mycobacterial KatG protein.

2. Which of the following is the most common manifestation of ocular sarcoidosis?

- A. Acute anterior uveitis
- B. Chronic anterior uveitis
- C. Acute posterior uveitis
- D. Chronic posterior uveitis
- E. Pan uveitis

Answer: B Chronic anterior uveitis, which is more common than acute uveitis, may have minimal symptoms. Uveitis can herald the nonocular signs of sarcoidosis and may precede the diagnosis of sarcoidosis by decades. Chronic anterior uveitis may lead to cataracts and glaucoma. Heerfordt syndrome consists of anterior uveitis accompanied by parotid gland enlargement and fever.

3. Which of the following best describes the role of transplantation in sarcoidosis?

- A. Transplantation should not be used because of the high frequency of disease recurrence.
- B. One- and 5-year graft survival rates for lung, liver, and heart are much less than for other diseases.
- C. One- and 5-year graft survival rates for lung, liver, and heart compare favorably with those of other diseases.
- D. Sarcoidosis accounts for more than 10% of all transplantations.

Answer: C Less than 1% of heart and liver and about 3% of lung transplantations are performed in patients with sarcoidosis. The 1- and 5-year graft survival rates for lung, liver, and heart transplantations in patients with sarcoidosis compare favorably with the results obtained for patients with other disorders.

1. Which one the following best characterizes the clinical picture of acute bronchitis and tracheitis?

- A. Absence of criteria for systemic inflammatory response syndrome
- B. Cough that lasts 1 to 3 weeks
- C. A syndrome that affects 5% of adults annually
- D. Most known causes are viral, yet antibiotics are prescribed in 70% of cases
- E. All of the above

Answer: E See Definitions, Epidemiology, and Clinical Manifestations sections. Acute bronchitis is common, with a cough lasting longer than most patients appreciate, and is usually caused by viruses. Too often, antibacterial antibiotics are prescribed.

2. Which one of the following statements is correct?

- A. Rapid diagnostic tests in general are relatively inexpensive and appear cost effective for outpatient use.
- B. Patients with acute bronchitis have significant declines of FEV1.
- C. Patients with atypical bacteria linked to acute bronchitis, such as *Mycoplasma* species, are seen earlier rather than later in their illness compared with those with viral etiologies.
- D. A procalcitonin level of less than 1 ng/L indicates a likely bacterial infection.
- E. Antibiotics have good efficacy in treating atypical organisms, such as *Mycoplasma* species, causing acute bronchitis.

Answer: B See Diagnosis section. In patients with acute bronchitis, significant declines in FEV1 cause many of their symptoms. Rapid diagnostic tests are expensive, and antibiotics are usually not helpful because most infections are caused by viruses. Polymerase chain reaction in fact has good reliability for identifying atypical infections, most of which are linked to patients seeking help later in their illnesses than those with viral infections. A low procalcitonin of less than 1 ng/L suggests infection caused by viruses.

3. Which one of the following statements is correct?

- A. Inflammation of the small airways is called bronchiolitis.
- B. Patients with acute bronchitis can have wheezing.
- C. Bronchiectasis is associated with permanent dilation of bronchi and chronic cough.
- D. Chronic bronchitis describes patients who have prolonged cough and sputum production for at least 3 months of the year for two consecutive years.
- E. All of the above

Answer: E See Definition section. This question is designed to distinguish the terms bronchiectasis and chronic bronchitis from acute bronchitis. Acute bronchitis can involve the small airways and cause wheezing. Isolated inflammation of the small airways is called bronchiolitis.

1. For which of the following groups is pneumococcal polysaccharide vaccine not routinely recommended?

- A. Otherwise healthy adults aged 50 to 65 years
- B. Adults aged 19 to 65 years who have immunocompromising conditions
- C. Cigarette smokers
- D. Adults with asthma
- E. Alcoholics, especially if liver disease is present

Answer: A The incidence of pneumococcal pneumonia is highest in persons younger than 2 years of age or older than 65 years of age. Thus, pneumococcal polysaccharide vaccine is not recommended for otherwise healthy adults aged 50 to 65 years. This vaccine is, however, recommended for persons who have immunocompromising conditions or lung disease (such as chronic obstructive pulmonary disease or asthma) and for persons who are cigarette smokers and heavy consumers of alcohol.

2. Which of the following is the least likely to be found as a cause for a syndrome consistent with community-acquired pneumonia?

- A. Pulmonary edema
- B. Pulmonary fibrosis
- C. Lung cancer
- D. *Nocardia* infection
- E. Influenza virus infection

Answer: D Pulmonary edema, pulmonary fibrosis, and lung cancer, although not infectious in origin, are frequent causes of a new pulmonary infiltrate, cough, and sputum production, sometimes accompanied by fever. In well-documented large case series, these symptoms and signs are only slightly more common in patients with bacterial pneumonia than in noninfectious conditions such as pulmonary edema, pulmonary fibrosis, or lung cancer. Whereas influenza virus is a major cause of hospitalization for pneumonia (often with secondary bacterial infection), *Nocardia* is an infrequent cause.

3. Which of the following contributes to a need for intensive unit care in a patient who is hospitalized for bacterial pneumonia?

- A. Confusion
- B. Serum creatinine elevated to twice baseline
- C. $P_{aO_2} = 90$ mm Hg
- D. White blood cell count < 6000 with 15% band forms
- E. All of the above

Answer: E Confusion, a rising serum creatinine, and a falling O_2 saturation indicate severe disease. In a patient with a bacteremia pneumonia, a low white blood cell count with increased band forms is an ominous sign that is associated with a 65% mortality in pneumococcal infections.

4. Which of the following conditions is not associated with an increased incidence or severity of pneumococcal pneumonia?

- A. Poorly controlled hypertension
- B. Diabetes mellitus
- C. Renal insufficiency
- D. Cirrhosis of the liver
- E. Multiple myeloma

Answer: A In multiple myeloma, the inability to produce normal immunoglobulins to new antigenic stimuli can result in pneumonia. The well-documented increased incidence of pneumonia in patients who have diabetes mellitus, renal insufficiency, and cirrhosis of the liver is multifactorial, with poor leukocyte function (migration, ingestion, and bacterial killing) as well as poor antibody responses contributing. In contrast, there is no relationship between hypertension and pneumonia.

1. A 20-year-old woman presents with a 2-day history of pleuritic chest pain and shortness of breath on exertion. She has no medical history, but she started on an oral contraceptive 6 weeks ago. Her chest radiograph is normal. Which of the following tests would you order?

- A. D-dimer
- B. Ventilation-perfusion lung scan
- C. Computed tomographic pulmonary angiogram
- D. Bilateral compression ultrasonography of the lower extremities
- E. Electrocardiogram

Answer: B The pretest probability of pulmonary embolism is high, so diagnostic testing is required to evaluate this possibility. With a normal chest radiograph, ventilation-perfusion lung scanning is likely to establish the diagnosis of pulmonary embolism and is preferred over computed tomographic pulmonary angiography in young women because there will be less radiation exposure to the breasts. A D-dimer test is not helpful in patients with a high pretest probability of pulmonary embolism because additional testing is needed regardless of whether the D-dimer is positive or negative. Although most pulmonary emboli arise from deep vein thrombosis in the lower extremities, compression ultrasonography is negative in at least 50% of patients with confirmed pulmonary embolism. The echocardiogram is not diagnostic in patients with pulmonary embolism (den Exter PL, Klok FA, Huisman MV. Diagnosis of pulmonary embolism: advances and pitfalls. *Best Pract Res Clin Haematol.* 2012;25:295-302; Komissarova M, Chong S, Frey K, et al. Imaging of acute pulmonary embolism. *Emerg Radiol.* 2013;20: 89-101).

2. A 68-year-old man underwent left knee arthroplasty 6 days ago and is receiving rivaroxaban (10 mg once daily) for thromboprophylaxis. He complains of shortness of breath while ambulating, and his oxygen saturation during these episodes decreases to 92%. A computed tomographic pulmonary angiogram reveals several segmental pulmonary emboli. Which of the following treatment strategies would facilitate his discharge home?

- A. Stop rivaroxaban and start warfarin; discharge him when his international normalized ratio (INR) is 2 or higher.
- B. Stop rivaroxaban, give enoxaparin in therapeutic doses, and start warfarin; discharge him when the INR is 2 or higher.
- C. Increase the dose of rivaroxaban to 15 mg twice daily and discharge him when he is clinically stable.
- D. Insert a retrievable filter and start warfarin; remove the filter when the INR is 2 or higher.

Answer: C This patient has suffered a pulmonary embolism despite thromboprophylaxis with rivaroxaban. With an episode of provoked pulmonary embolism, he requires 3 months of anticoagulant therapy. Increasing the rivaroxaban dose from the prophylactic dose of 10 mg once daily to the treatment dose of 15 mg twice daily offers the simplest therapy. After 3 weeks, the rivaroxaban dose can be decreased to 20 mg once daily. Warfarin alone is inadequate because of its delayed onset of action. An overlap of enoxaparin with warfarin is an alternative option, but this strategy would require subcutaneous injection of enoxaparin for at least 5 days, and the warfarin would require INR monitoring and dose adjustments (Agnelli G, Becattini C. Acute pulmonary embolism. *N Engl J Med.* 2010;363:366-274; Vanassche T, Verhamme P. Rivaroxaban for the treatment of pulmonary embolism. *Adv Ther.* 2013;30:589-606).

3. A 60-year-old woman is receiving chemotherapy for metastatic breast cancer. A staging computed tomographic scan reveals multiple pulmonary emboli in segmental arteries. She is asymptomatic. Which of the following treatments is the best?

- A. Give dalteparin and transition her to warfarin.
- B. Give dalteparin and continue it at least as long as she is receiving chemotherapy.
- C. Give rivaroxaban.

D. Give warfarin.

E. No therapy.

Answer: B Patients who have cancer and who develop multiple incidental pulmonary emboli require treatment. Low-molecular-weight heparin is better than warfarin for the prevention of recurrence in such patients. Although rivaroxaban and apixaban appear to be as effective as conventional anticoagulation for the treatment of patients with pulmonary embolism, they have not been extensively evaluated in patients with cancer, nor have they been compared with low-molecular-weight heparin in cancer patients (Lyman GH, Khorana AA, Kuderer AM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2013;31:2189-2204; Farge D, Deboureaud P, Beckers M, et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *J Thromb Haemost*. 2013;11:56-70).

4. A 32-year-old woman has been diagnosed with pulmonary embolism in her second trimester of pregnancy. Which of the following treatments would you prescribe?

A. Warfarin

B. Rivaroxaban

C. Unfractionated heparin

D. Low-molecular-weight heparin

E. Fondaparinux

Answer: D Warfarin and rivaroxaban cross the placenta and can cause fetal anomalies and/or fetal bleeding. Therefore, these agents should be avoided in pregnancy. Neither unfractionated nor low-molecular-weight heparin crosses the placenta, but low-molecular-weight heparin is preferred because it can be given once daily and is associated with a lower risk for heparin-induced thrombocytopenia and osteoporosis than is unfractionated heparin. Because there is less information about the safety of fondaparinux in pregnancy, it should be reserved for patients with a history of heparin-induced thrombocytopenia or an allergy to low-molecular-weight heparin (Fogerty AE, Connors JM. Treating venous thromboembolism in pregnancy. *Hematol Oncol Clin North Am*. 2011;25:379-391; Arya R. How I manage venous thromboembolism in pregnancy. *Br J Haematol*. 2011;153:698-708).

5. A 38-year-old previously healthy woman presents to the emergency department with a 7-day history of low-grade fever, shortness of breath on exertion, and nonproductive cough. Her heart rate is 90 beats/min, her oxygen saturation on room air is 98%, and her chest radiograph is normal. Which of the following tests would help to exclude the diagnosis of pulmonary embolism?

A. Bilateral compression ultrasound examination of the lower extremities

B. D-dimer

C. Electrocardiogram

D. Computed tomographic pulmonary angiogram

E. Ventilation-perfusion lung scan

Answer: B This patient has no risk factors for pulmonary embolism, so her pretest probability is low. Therefore, a negative D-dimer test will help to exclude the diagnosis and will obviate the need for further investigation (Agnelli G, Becattini C. Acute pulmonary embolism. *N Engl J Med*. 2010;363:366-274; den Exter PL, Klok FA, Huisman MV. Diagnosis of pulmonary embolism: advances and pitfalls. *Best Pract Res Clin Haematol*. 2012;25:295-302).

1. A patient complains of orthopnea and dyspnea when bending. What is the best test to evaluate the possibility of bilateral diaphragm paralysis (BDP)?

- A. Obtain a chest radiograph
- B. Measure vital capacity
- C. Measure upright and supine vital capacity
- D. Measure transdiaphragmatic pressure
- E. Perform a sniff test with fluoroscopic imaging

Answer: D The diagnosis of BDP can be confirmed by measurements of transdiaphragmatic pressure (Pdi). There is no change in Pdi during inspiration with bilateral diaphragm paralysis. Vital capacity is reduced with BDP and is further reduced by 30 to 50% when the patient is in the supine position; however, these findings are not specific for BDP. Chest radiographs and sniff tests are not useful when diagnosing BDP. Unilateral diaphragm paralysis may be present when there is an elevated hemidiaphragm on a chest radiograph. The diagnosis of unilateral paralysis can be confirmed by performing a “sniff test” using fluoroscopy or ultrasound: paradoxical (cephalad) movement of the hemidiaphragm dome occurs during a sniff maneuver. An alternate diagnostic test for BDP or unilateral paralysis is performing two-dimensional ultrasound of the diaphragm in the zone of apposition. The diaphragm does not thicken with inspiration when the diaphragm is paralyzed.

2. Which disease of the chest wall causes the greatest restrictive impairment?

- A. Morbid obesity
- B. Ankylosing spondylitis
- C. Kyphoscoliosis
- D. Pectus excavatum

Answer: C Kyphoscoliosis produces the most severe restrictive impairments. Total lung capacity and vital capacity may be reduced to as low as 30% of predicted values. The restriction is more severe as the degree of spinal angulation increases and when there is respiratory muscle weakness. Morbid obesity may be accompanied by mild to moderate restriction when the patient’s body mass index is greater than 40 kg/m². Ankylosing spondylitis and pectus excavatum result in little or no restriction.

3. A patient is admitted with pneumonia and a large pleural effusion. Which feature is most consistent with the presence of a complicated parapneumonic effusion?

- A. Free-flowing pleural fluid on computed tomography of the chest
- B. Pleural fluid-to-serum protein ratio > 0.5
- C. Pleural fluid pH < 7.2
- D. Pleural fluid glucose > 60 mg/dL
- E. Pleural fluid-to-serum lactate dehydrogenase (LDH) ratio higher than 0.6,

Answer: C Complicated effusions are characterized by a pH of less than 7.2 and often have a low glucose content (<60 mg/dL). These effusions often require drainage to prevent formation of an empyema, cutaneous fistulas, bronchopleural fistulas, or fibrothorax. A pleural fluid-to-serum protein ratio of more than 0.5, a pleural fluid-to-serum LDH ratio of greater than 0.6, or a pleural fluid LDH concentration higher than two thirds the normal serum value indicates the presence of an exudate. Complicated parapneumonic effusions are exudates, but exudative effusions can be observed in inflammatory states or neoplasms and are not specific for infection. Parapneumonic effusions, which are the most common type of exudative pleural effusion, can occur in up to 40% of patients with pneumonia. An empyema is present when frank pus is aspirated from the pleural space, when Gram stain of the fluid is positive for bacteria, or when bacteria are cultured from the fluid.

4. A 26-year-old nonsmoking man presents with fever and chills. A chest radiograph demonstrates no infiltrate, but a widened mediastinum is noted. Computed tomography shows a middle mediastinal mass. The most likely diagnosis is which of the following?

- A. Thymoma
- B. Lymphoma
- C. Lung cancer
- D. Schwannoma

Answer: B Classifying the location of mediastinal masses as anterior, middle, or posterior mediastinum aids in the differential diagnosis. A middle mediastinal mass accompanied by systemic symptoms such as fever, night sweats, and weight loss is most consistent with lymphoma. Lung cancer with metastasis to mediastinal nodes is possible, but the patient's age and lack of smoking history make this diagnosis unlikely. Thymomas, germ cell tumors (teratomas), and thyroid tissue usually involve the anterior compartment. Neurogenic tumors, such as schwannomas, are typically seen in the posterior compartment. Mediastinal masses may be accompanied by symptoms including chest pain, cough, hoarseness, stridor, dysphasia, and dyspnea, but most often patients with mediastinal masses are asymptomatic.

5. The following statements are true regarding pneumothorax except which one?

- A. Pleural pressure becomes more subatmospheric, thereby resulting in compression of the underlying lung.
- B. A tension pneumothorax produces a mediastinal shift and hemodynamic compromise.
- C. Diagnosis can be made by obtaining an upright chest radiograph or a point-of-care ultrasound.
- D. Tube thoracostomy and suction followed by water-seal drainage are not always needed.
- E. Pneumothorax may occur spontaneously in individuals without a history of underlying lung disease or trauma.

Answer: A Normally, the pressure within the pleural space is slightly subatmospheric. However, when more than a very small amount of air accumulates within the pleural space, pressure within the pleural space becomes positive, and underlying lung is compressed. Pneumothorax is often associated with blunt or penetrating trauma, but it may occur spontaneously in some patients (typically tall, young, thin men) without underlying lung disease. Air within the pleural space appears as an area of lucency on the chest radiograph or lack of the "sliding lung sign" on ultrasound. A tension pneumothorax produces mediastinal shift and requires immediate tube thoracostomy. If the pneumothorax is small and the patient is not in distress, tube thoracostomy is not needed, and observation alone may be sufficient.

1. A hypertensive and obese 55-year-old man, now 2 days after a hip fracture reduction, has nocturnal ventricular tachycardia and complains of an inability to maintain consolidated sleep. The nursing staff reports that he has very loud and crescendo snoring when he sleeps. What is the best immediate recommendation in this setting?

- A. Extended-release nonbenzodiazepine sedative-hypnotic at bedtime
- B. Increased doses of opioid analgesics to improve pain control
- C. Nocturnal oxygen supplementation via Venturi mask, titrated to achieve an oxygen saturation of hemoglobin (Spo₂) of more than 92%
- D. Intracardiac electrophysiology study (EPS)
- E. Bedside diagnostic polysomnography with positive airway pressure titration

Answer: E The most likely diagnosis is obstructive sleep apnea, which has been exacerbated by sedative and opioid medications. A trial of continuous positive airway pressure (CPAP) is indicated.

2. Which of the following patients is *not* likely to have a higher prevalence of obstructive sleep apnea than the general adult male population?

- A. An 85-year-old man with a normal body mass index (BMI) and borderline systemic hypertension
- B. A 50-year-old man with a normal BMI and stable heart failure
- C. A 60-year-old morbidly obese woman with no known lung disease but with hypoventilation when awake
- D. A 40-year-old man with cystic fibrosis and a normal BMI
- E. A 55-year-old man 1 week following acute myocardial infarction

Answer: D Cystic fibrosis is not known to be directly associated with a higher prevalence of obstructive sleep apnea.

3. Current recommendations for reducing the risk associated with driving owing to sleepiness in patients with obstructive sleep apnea includes which of the following?

- A. Increased nocturnal sleep time
- B. CPAP
- C. Armodafinil
- D. Strategic napping
- E. Fluoxetine

Answer: B CPAP is currently the only recommended treatment for reducing driving risk in patients with obstructive sleep apnea (Strohl KP, Brown DB, Collop N et al. An official American Thoracic Society Clinical Practice Guideline: sleep apnea, sleepiness, and driving risk in noncommercial drivers. An update of a 1994 Statement. *Am J Respir Crit Care Med.* 2013;187: 1259-1266).

Ch / 101 **INTERVENTIONAL AND SURGICAL APPROACHES TO LUNG DISEASE**

1. Which of the following statements is correct concerning endobronchial ultrasound (EBUS)?

- A. The use of EBUS obviates the need for surgical lymph node sampling.
- B. EBUS can provide adequate material for the analysis of molecular markers in patients with non-small cell lung cancer.
- C. Radial-probe EBUS allows for real-time sampling of hilar lymph nodes.
- D. The combined use of RP-EBUS and navigation bronchoscopy has a yield equivalent to transthoracic needle biopsy for the diagnosis of a 2-cm pleural-based nodule.
- E. All of the above

Answer: B EBUS can obtain adequate material for the evaluation of tumor molecular markers in more than 94% of cases. Although EBUS has very high sensitivity and specificity, specimens showing lymphocytes but no tumor may need to be confirmed as true negatives by surgical lymph node dissection. Radial-probe EBUS is primarily used to identify parenchymal nodules. Transthoracic needle biopsy is associated with a higher diagnostic yield for peripheral nodules but is more likely to be complicated by the development of pneumothorax compared with radio-probe EBUS and navigation bronchoscopy.

2. Which of the following statements is true concerning patients with severe emphysema?

- A. Bronchoscopic lung volume reduction can reduce emergency department visits for exacerbations of chronic bronchitis.
- B. The use of oxygen and surgical lung volume reduction has been shown to decrease mortality.
- C. Surgical lung volume reduction is better than medical therapy for patients with homogenous emphysema.
- D. Surgical lung volume reduction improves mortality in the subset of patients with high exercise tolerance.
- E. All of the above

Answer: B The use of oxygen and surgical lung volume reduction improves mortality in appropriately selected patients with advanced emphysema: patients with upper lobe-predominant disease, an FEV1 of less than 20%, and low exercise capacity. For patients with good exercise tolerance, surgical lung volume reduction increases mortality compared with standard medical therapy. There are no data suggesting that bronchoscopic lung volume reduction reduces emergency room visits for exacerbations of chronic obstructive pulmonary disease.

3. Which of the following statements is correct concerning lung transplantation?

- A. The outcomes of unilateral lung transplantation are better than for bilateral lung transplantation.
- B. Lung transplantation improves survival in patients with advanced emphysema.
- C. Infection with *Aspergillus* species is a common cause of mortality at 5 years.
- D. The bronchiolitis obliterans syndrome is the leading cause of late mortality.
- E. All of the above

Answer: D Bilateral lung transplantation has improved outcomes compared with unilateral transplantation. Transplantation confers no overall survival advantage in patients with advanced emphysema, and obliterative bronchiolitis is the leading cause of mortality at 5 years.

4. Which of the following are true concerning central airway obstruction?

- A. The treatment of malignant central airway obstruction does not affect mortality.
- B. Laser photoresection is better than argon plasma coagulation to treat malignant central airway obstruction.
- C. Airway stenting is the procedure of choice for extrinsic airway obstruction.
- D. Airway stents are well tolerated and associated with minimal complications.
- E. All of the above

Answer: D Airway stents are the only endoscopic treatment that can palliate extrinsic airway obstruction. They are, however, associated with significant complications. After successful treatment of malignant airway obstruction, patients have mortality rates similar to those of patients with malignancy but no central airway obstruction.

1. Optimal models for the care of critically ill patients include all except which of the following?

- A. Critical care delivered by a dedicated intensivist or obligatory intensivist consultation on all intensive care unit (ICU) patients
- B. Nighttime in-house intensivist coverage
- C. Intensivist-led multidisciplinary rounds
- D. A multidisciplinary team with explicitly defined roles
- E. Use of a “best practices” checklist or equivalent tool on rounds

Answer: B Strategies considered to optimize the process of critical care include a closed ICU model with intensivists delivering the care or consulting on each patient, intensivist-led multidisciplinary rounds in which clinicians have explicitly defined roles, and rounds that incorporate a best practices tool. Randomized trial evidence does not show an impact of 24/7 in-house intensivist coverage in fully staffed academic ICUs.

2. Compared with crystalloids for fluid maintenance or fluid resuscitation, which statement is true regarding starch solutions?

- A. Starch decreases the risk of renal failure.
- B. Starch increases the probability of needing renal replacement therapy.
- C. Starch increases the probability of needing renal replacement therapy, but only in patients with severe sepsis.
- D. Starch increases the risk of death in patients with severe sepsis.
- E. Both B and D.

Answer: E Starches do not decrease the risk of renal failure. Large randomized trials show that in both general ICU patients and in patients with severe sepsis, starches increase the probability of needing renal replacement therapy; furthermore, in patients with severe sepsis, resuscitation with starches increases the risk of death.

3. For mechanically ventilated patients receiving infusions of sedation or analgesia, which of the following statements is true?

- A. Concerns prevail that oversedation may induce delirium, prolonged weakness, and delayed liberation from the ventilator.
- B. Nurse-led targeted sedation protocols represent an effective method to minimize the chance of oversedation while maintaining the patient’s comfort.
- C. Compared with continuing infusions, daily interruption of sedation infusions decreases the duration of ventilation and ICU stay.
- D. Daily interruption of sedation infusions appears to have no additional impact on the duration of mechanical ventilation or safety of the patient if a nurse-led targeted sedation protocol is in place.
- E. All of the above.

Answer: E Concern is emerging about the adverse effects of prolonged sedation and analgesia infusions. Targeted sedation by a nurse-led protocol represents an optimal approach to minimize unnecessary sedation. Daily interruption of sedation infusions is also effective but may not further improve outcomes if individualized, targeted sedation levels are already managed with a nurse-led protocol.

4. Which of the following statements is not true regarding the legacy of critical illness?

- A. Disability among survivors of critical illness is pervasive, affecting many domains of quality of life.
- B. Disability among ICU survivors increases the overall length of hospital stay.
- C. Disability among family caregivers of ICU survivors is rare.
- D. Some aspects of disability among ICU survivors may be mitigated by earlier rehabilitation in the ICU.
- E. Combined early physiotherapy, sedation interruption, and spontaneous breathing tests used in combination have been shown to improve survival in critically ill patients.

Answer: C Depression, anxiety, and post-traumatic stress disorder are common in family caregivers of ICU survivors, and ICU survivors themselves can have pervasive, long-lasting multidimensional disabilities. Some disabilities are targets for early physical rehabilitation; others may benefit from counseling and other supports. Coordinated multidisciplinary approaches to help patients along the trajectory to recovery include early physiotherapy, daily sedation interruptions, and spontaneous breathing tests.

5. Which of the following statements about end-of-life care in the ICU is true?

- A. Palliative care is exclusively patient centered.
- B. Optimal end-of-life care is focused primarily on complete, timely management of symptoms in the final days.
- C. Decisions to withdraw life support are primarily determined by acute and chronic physiologic trends during critical illness.
- D. Dignified end-of-life care involves caring for patients in a manner consistent with their values when they cannot speak for themselves.
- E. In contemporary ICUs, death is more commonly preceded by withdrawal of inotropes and vasopressors than by withdrawal of mechanical ventilation.

Answer: D Palliative care in the ICU ensures the patient's dignity, is holistic, is both patient and family centered, and addresses broad dimensions of health. Mechanical ventilation is the most common life support administered and withdrawn in the ICU. Decisions to withdraw mechanical ventilation are based less on pathophysiology than on the patient's values, which are typically expressed by the family, and physicians' predictions about future quality of life.

Ch / 103 RESPIRATORY MONITORING IN CRITICAL CARE

1. P_{aCO_2} (arterial carbon dioxide tension) is determined by

- A. CO_2 production rate and minute ventilation
- B. Carbonic anhydrase level and alveolar ventilation
- C. CO_2 production rate and alveolar ventilation
- D. Diffusing capacity and CO_2 production rate
- E. Minute ventilation and dead space (V_d/V_t)

Answer: C The P_{aCO_2} is determined by the rate of CO_2 production and the alveolar ventilation.

2. A patient's ambient air arterial blood gas shows a P_{aO_2} of 60 torr and a P_{aCO_2} of 60 torr (at sea level). What is this patient's alveolar-arterial oxygen gradient?

- A. 4 torr
- B. 14 torr
- C. 24 torr
- D. 34 torr
- E. 37 torr

Answer: B The alveolar-arterial oxygen gradient at sea level (barometric pressure = 760 mm Hg) is calculated as $149 - ([1.25] P_{aCO_2} + P_{aO_2})$. The alveolar-arterial oxygen gradients with these arterial blood gas values = 14 torr (or mm Hg).

3. Variables that affect the ratio of dead space to tidal volume (V_d/V_t) include

- A. End-tidal CO_2 and P_{aCO_2}
- B. Exhaled CO_2 tension (P_{eCO_2}) and P_{aO_2}
- C. P_{aO_2} and CO_2 production rate
- D. Exhaled CO_2 tension (P_{eCO_2}) and P_{aCO_2}
- E. Exhaled CO_2 tension (P_{eCO_2}) and end-tidal CO_2 tension

Answer: D The V_d/V_t is calculated by the Bohr equation, which is $(P_{aCO_2} - P_{eCO_2})/P_{aCO_2}$.

Ch / 104 **ACUTE RESPIRATORY FAILURE**

1. Which of the following mechanisms can lead to a reduction in the arterial oxygen tension (P_{aO_2})?

- A. Ventilation-perfusion mismatch
- B. Intrapulmonary right-to-left shunt
- C. Decreased inspired partial pressure of oxygen
- D. Alveolar hypoventilation
- E. All of the above

Answer: E It is important for clinicians to understand the physiologic mechanisms of arterial hypoxemia. Once the physiologic basis of hypoxemia is known, the differential diagnosis as to specific cause (i.e., the type of disease at hand leading to this physiologic abnormality) can be made, and a specific treatment often can be initiated.

2. If a patient has the clinical presentation of bilateral pneumonia with no evidence of cardiac disease and has a chest radiograph that shows bilateral pulmonary infiltrates, which of the following P_{aO_2}/F_{iO_2} ratios (where P_{aO_2} is in mm Hg) is consistent with the diagnosis of acute respiratory distress syndrome (ARDS)?

- A. $P_{aO_2} = 80$; $F_{iO_2} = 0.25$
- B. $P_{aO_2} = 200$; $F_{iO_2} = 0.3$
- C. $P_{aO_2} = 200$; $F_{iO_2} = 0.8$
- D. $P_{aO_2} = 190$; $F_{iO_2} = 0.3$
- E. $P_{aO_2} = 490$; $F_{iO_2} = 0.5$

Answer: C It is the only one with a P_{aO_2}/F_{iO_2} ratio of less than 300 mm Hg. It is important to be able to calculate the P_{aO_2}/F_{iO_2} ratio to make the diagnosis of ARDS in a patient who has bilateral pulmonary infiltrates consistent with pulmonary edema but no evidence of cardiogenic pulmonary edema as the primary cause.

3. Which of the following treatments has been shown to reduce mortality in patients with ARDS on the basis of multicenter randomized trials.

- A. High-frequency ventilation
- B. Lung-protective ventilation with a tidal volume of 6 mL/kg predicted body weight and a plateau airway pressure of less than 30 cm H₂O
- C. Intermittent mandatory ventilation with weaning to pressure support ventilation
- D. Pressure-control ventilation
- E. Liquid ventilation with perfluorocarbons

Answer: B on the basis of a National Heart, Lung, and Blood Institute– sponsored ARDS Network clinical trial in 2000. All intensivists need to know that lung-protective ventilation with this strategy markedly reduces mortality in patients with ARDS.

4. Why do most patients with an exacerbation of chronic obstructive pulmonary disease (COPD) require relatively low-flow nasal oxygen to achieve adequate oxygenation?

- A. Because intrapulmonary right-to-left shunt is an important cause of the hypoxemia
- B. Because there are many lung units with low ventilation-perfusion ratios, and these units are the primary cause of arterial hypoxemia in these patients
- C. Because diffusion impairment is an important cause of hypoxemia and COPD
- D. Because the inspired oxygen tension is low in these patients
- E. Because such patients have decreased cardiac output and therefore low perfusion

Answer: B because ventilation-perfusion abnormalities predominate. In most patients with an exacerbation of COPD, most gas exchange takes place in units with low ventilation to perfusion values. In most patients, the hypoxemia can be corrected, at least in part, with low-flow oxygen. Clinicians should understand the physiologic basis of treating an exacerbation of COPD, which normally requires low-flow oxygen unless another process, such as pneumonia, pulmonary edema, or atelectasis, could be causing an intrapulmonary shunt.

5. Which of the following clinical conditions have been associated with the development of ARDS?

- A. Nonpulmonary sepsis
- B. Pneumonia
- C. Drug overdose
- D. Massive blood transfusions
- E. All of the above

Answer: E Clinicians need to know clinical disorders that may be associated with ARDS.

Ch / 105 **MECHANICAL VENTILATION**

1. Which of the following is not usually a goal when positive end-expiratory pressure (PEEP) is used in patients with the acute respiratory distress syndrome (ARDS)?

- A. Decrease the negative physiologic consequences of auto-PEEP
- B. Recruit alveolar regions
- C. Decrease ventilator-induced lung injury
- D. Increase oxygenation
- E. Increase functional residual capacity

Answer: A Although external PEEP may be useful in some patients with auto-PEEP, especially when it is caused by airway obstruction, this problem usually is not an issue in patients with ARDS.

2. Which of the following is not an exclusion criterion for use of noninvasive ventilation with COPD?

- A. Facial trauma
- B. Apnea
- C. Hypercapnia
- D. Loss of consciousness
- E. Hemodynamic instability

Answer: C Hypercapnia is not a contraindication to the use of noninvasive ventilation in patients with COPD. In fact, COPD is one of the indications for its use. Noninvasive ventilation should not be used in most patients with severe facial trauma, because of the problems of fitting the mask, or in patients who are unconscious or apneic, because a patient has to be able to breathe spontaneously to trigger the ventilator. In addition, patients with hemodynamic compromise commonly need full respiratory support to minimize the oxygen cost of breathing.

3. Which of the following is not first-line therapy for a patient who has ARDS and a P/F ratio below 100 mm Hg?

- A. Lung-protective mechanical ventilation
- B. Use of the prone position
- C. Neuromuscular blocking agents
- D. High-frequency ventilation
- E. Use of PEEP

Answer: D Two recent studies have shown that high-frequency ventilation does not have a role in the treatment of adult patients with ARDS early in their course.

4. Which of the following is an indication *not* to try a spontaneous breathing trial?

- A. A Pao₂ = 88 mm Hg while breathing an Fio₂ = 1.0
- B. PEEP = 5 mm Hg
- C. Patient is not receiving vasopressors
- D. Patient is alert
- E. Patient is receiving minimal sedation

Answer: A In general, it is best not to attempt a spontaneous breathing trial if the patient has a P/F ratio below 200 mm Hg.

5. Which of the following statements about lung-protective strategy is incorrect?

- A. Ventilator-induced lung injury can be associated with release of a number of mediators that may have systemic consequences.
- B. Regional lung distention is an important factor in causing ventilator-induced lung injury.
- C. Use of a lung-protective strategy is important even in patients who do not have ARDS.
- D. An increased plateau pressure (>~30 cm H₂O) always indicates that the patient is at increased risk of ventilator-induced lung injury.
- E. The use of a lung-protective strategy in an ARDS patient has been shown to decrease mortality.

Answer: D The key variable in terms of overdistention for ventilator-induced lung injury is overdistention of regional lung units. A patient may have an increased plateau pressure because of conditions that affect chest wall mechanics (e.g., ascites), and if so, the high plateau pressure may not indicate that the lung is being overstretched.

1. Hydroxyethyl starch fluid resuscitation is associated with

- A. Less renal failure
- B. Better outcomes
- C. Higher mortality
- D. Lowers costs of fluid replacement
- E. Lowered plasma oncotic pressure

Answer: C Hydroxyethyl starch has increasingly been shown to increase morbidity and mortality in shock.

2. Which vasoactive agent is the least likely to increase heart rate?

- A. Dopamine
- B. Epinephrine
- C. Phenylephrine
- D. Dobutamine
- E. Nitroprusside

Answer: C Phenylephrine is a pure α agonist and does not have β -adrenergic activity that precipitates tachycardia.

3. A decreased central venous or mixed venous oxygen saturation is seen in all except which of the following?

- A. Cardiogenic shock
- B. Severe cyanide poisoning
- C. Hemorrhagic shock
- D. During cardiopulmonary resuscitation
- E. Saddle pulmonary embolus

Answer: B Cyanide poisoning is the correct answer. This type of poisoning uncouples oxidative metabolism, so less oxygen is extracted from blood, thereby leading to an increased mixed venous oxygen content.

4. Obstructive shock can result from each of the following except which one?

- A. Pericardial tamponade
- B. Tension pneumothorax
- C. Pulmonary embolus
- D. Increased arterial vascular resistance
- E. Ventricular septal defect

Answer: E A ventricular septal defect does not obstruct the flow of blood, whereas all other choices represent physiologic conditions in which obstruction can occur.

5. Shock can be accompanied by

- A. Hypovolemia
- B. Myocardial suppression
- C. Vasodilation
- D. Normal or increased lactate level
- E. All of the above

Answer: E All of the noted items are associated with shock.

1. Which of the following is the most common cause of cardiogenic shock?

- A. Pump failure in acute myocardial infarction
- B. Myocarditis
- C. Mechanical complications of acute myocardial infarction
- D. Right ventricular infarction
- E. Valvular heart disease

Answer: A The predominant cause of cardiogenic shock is left ventricular failure secondary to acute myocardial infarction. The other listed answers can lead to cardiogenic shock but are less common.

2. Coronary angiography in patients with cardiogenic shock in the setting of acute myocardial infarction most commonly shows which of the following?

- A. Left main coronary artery disease
- B. Single-vessel left anterior descending coronary artery disease
- C. Multivessel disease
- D. Extensive collateralization
- E. Two-vessel disease involving the right coronary artery

Answer: C In cardiogenic shock resulting from acute myocardial infarction, coronary angiography most often demonstrates multivessel disease. About 30% of patients have a left main coronary artery occlusion, about 60% have three-vessel coronary disease, and only about 20% have single-vessel disease.

3. Which of the following is true concerning the use of vasopressor agents in cardiogenic shock?

- A. Norepinephrine is more arrhythmogenic than dopamine.
- B. Norepinephrine is associated with decreased 28-day mortality compared with dopamine in patients with cardiogenic shock.
- C. Dopamine is preferable because it improves renal function.
- D. Dobutamine is more effective at raising blood pressure.
- E. Blood pressure should be monitored noninvasively to avoid vascular complications.

Answer: B In a randomized trial of patients with shock, norepinephrine reduced 28-day mortality in a prespecified subgroup of patients with cardiogenic shock compared with dopamine. Dopamine was more arrhythmogenic and does not improve renal function in patients with shock, although some patients have increased urine output. Dobutamine has vasodilatory effects and can worsen hypotension. Noninvasive blood pressure monitoring can be unreliable in patients with shock; arterial line placement is recommended.

4. Complete the following statement correctly: Percutaneous left ventricular assist devices for cardiogenic shock

- A. Improve hemodynamics compared with intra-aortic balloon pumping.
- B. Improve 30-day mortality compared with intra-aortic balloon pumping.
- C. Should be reserved for patients eligible for cardiac transplantation.
- D. Are associated with decreased vascular complication rates compared with intra-aortic balloon pumping.
- E. Provide support independent of right ventricular function.

Answer: A Percutaneous left ventricular assist devices (LVADs) provide short-term hemodynamic support after cardiogenic shock. By allowing time for left ventricular recovery, they are usually intended as a bridge to definitive therapy, such as transplantation. Percutaneous LVADs provide better hemodynamics compared with an intra-aortic balloon pump, with higher cardiac indices and mean arterial pressures as well as lower filling pressures; however, they have not been shown to

improve mortality at 30 days. Known complications of percutaneous LVADs include limb ischemia and bleeding. The available percutaneous devices support the left ventricle and thus require adequate right ventricular function.

5. Which of the following is true concerning prognosis after cardiogenic shock in the setting of myocardial infarction?

- A. Hemodynamics predict long-term mortality among patients undergoing revascularization.
- B. The early survival benefits of revascularization are lost by 5-year follow-up.
- C. Benefits of revascularization are seen only in younger patients.
- D. Prognosis is worse than in patients with end-stage nonischemic myocardial disease.
- E. Quality of life in survivors is usually excellent.

Answer: E The quality of life in survivors of cardiogenic shock complicating acute myocardial infarction is usually excellent, with 83% of patients either asymptomatic or having only mildly symptomatic heart failure. Hemodynamics predict short-term but not long-term mortality. The survival benefit of early revascularization is maintained at 6-year follow-up, with 5-year survival approaching 45%. Among patients undergoing revascularization, age and time to revascularization predict survival, but the benefits of revascularization are seen at every level of risk, with an average 1-year survival of 50 to 55%. For patients with end-stage nonischemic myocardial disease, the prognosis is very poor in the absence of heart transplantation.

1. Which of the following statements about dopamine in septic shock is correct?

- A. Low-dose dopamine is effective in decreasing the risk of acute kidney injury.
- B. Dopamine infusion was associated with increased cardiovascular adverse effects compared with norepinephrine in a large mortality-powered randomized controlled trial.
- C. Dopamine increases mean arterial pressure excessively compared with norepinephrine.
- D. Dopamine alters dopaminergic receptor neurologic functions and alters mental status in septic shock.
- E. Randomized controlled trial evidence shows that dopamine infusion shortens the duration of vasopressor support compared with norepinephrine.

Answer: B Dopamine infusion is associated with increased cardiovascular adverse effects compared with norepinephrine (De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of septic shock. *N Engl J Med*. 2010;362:779-789; Patel GP, Grahe JS, Sperry M, et al. Efficacy and safety of dopamine versus norepinephrine in the management of septic shock. *Shock*. 2010;33:375-380.). Low-dose dopamine does not decrease the risk of acute kidney injury (Bellomo R, Chapman M, Finfer S, et al. Australian and New Zealand Intensive Care Society Clinical Trials Group. Low dose dopamine in patients with early renal dysfunction: a placebo controlled randomised trial. *Lancet*. 2000;356:2139-2143.) and is not recommended in the surviving sepsis guidelines (Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41:580-637.) for this reason. There is no convincing evidence that dopamine increases mean arterial pressure excessively compared with norepinephrine; both are given as continuous infusions that can be effectively titrated to a target mean arterial pressure. Although there are dopaminergic neurons, there is no evidence that dopamine infusion alters dopaminergic receptor neurologic functions or alters mental status in septic shock. There is no evidence that dopamine shortens the duration of vasopressor support compared with norepinephrine (De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of septic shock. *N Engl J Med*. 2010;362:779-789.).

2. Septic shock has not been shown to be associated with which of the following complications during post-hospitalization recovery?

- A. Cognitive dysfunction
- B. Decreased long-term survival
- C. Neuromuscular dysfunction
- D. Impaired quality of life
- E. Recurrent seizure disorder

Answer: E Cognitive function, long-term survival, neuromuscular function, and quality of life are all reduced among survivors of severe sepsis. However, survivors of septic shock do not have increased risk of recurrent seizures. (Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med*. 2013;369:1306-1316. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364:1293-1304. Iwashyna TJ, Ely EW, Smith DM, et al. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304:1787-1794.)

1. Frostbite is a limb-threatening injury that requires early intervention for limb preservation. Which of the following interventions is not currently routinely recommended for the management of deep frostbite?

- A. Update tetanus status as required
- B. Prophylactic coverage with systemic antibiotics
- C. Early and rapid rewarming of frozen tissue
- D. Administration of low-dose nonsteroidal anti-inflammatory drugs until wound healing is complete
- E. None of the above

Answer: B Frostbite is a limb-threatening injury that requires urgent intervention. Recently developed guidelines no longer include routine prophylactic antibiotics. Antibiotic therapy, however, is strongly recommended at the earliest signs of infection. Rewarming remains the cornerstone of therapy for frostbite. Updating tetanus status and using nonsteroidal anti-inflammatory drugs to mitigate inflammation also are recommended.

2. The management of hypothermia requires attention to detail, including careful patient handling and judicious hydration, to avoid triggering of potential fatal arrhythmias. If a patient with hypothermia develops a life-threatening arrhythmia, which treatment approach best describes current guidance on defibrillation?

- A. Ventricular fibrillation in the hypothermic patient is unresponsive to defibrillation, so the patient should be treated with chest compressions until normal core body temperature is achieved.
- B. Defibrillation equipment is unreliable in a hypothermic patient.
- C. Antiarrhythmic medications should be used aggressively until normal body temperature is achieved, and if there is no response, continue cardiopulmonary resuscitation until return of a normal core temperature.
- D. For the hypothermic patient with a temperature lower than 30° C, a single defibrillation attempt is warranted. If this attempt fails, proceed with basic life support guidelines with defibrillation attempts as required while pursuing active rewarming.

Answer: D The success rate of defibrillation and of life-saving medications in a cardiac arrest scenario is mitigated in the presence of significant hypothermia. If ventricular tachycardia (VT) or ventricular fibrillation (VF) is present, defibrillation should be attempted. If VT or VF persists after a single shock, the value of subsequent defibrillations until a target temperature is achieved is uncertain. It may be reasonable to perform further defibrillation attempts according to the standard basic life support algorithm concurrent with rewarming strategies. (Vanden Hoek TL, Morrison LJ, Shuster M, et al. Part 12: cardiac arrest in special situations: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122:S829-S861.)

3. When exertional heat stroke is suspected, what should be the first treatment priority?

- A. Measuring rectal/core temperature
- B. Starting an intravenous line for fluid resuscitation and drug delivery
- C. Determining mental status
- D. Removing the patient's clothes
- E. Rapid whole body cooling with immersion in cooled or ice water

Answer: E Exertional heat stroke is a life-threatening emergency. Although assessing mental status, obtaining intravenous access for fluid administration, and determining the core temperature with a rectal thermometer are all important interventions, the cornerstone of therapy that should be an immediate focus is rapid cooling, which is best facilitated by rapid whole body cooling with immersion in cooled or ice water. (Casa DJ, Almquist J, Anderson SA, et al. The inter-association task force for preventing sudden death in secondary school athletics programs: best-practices recommendations. *J Athl Train*. 2013;48:546-553.)

1. A patient presents to the emergency department with a metabolic acidosis after exposure to a toxin. For which one of the following toxic etiologies is hemodialysis indicated?

- A. Acetaminophen
- B. Aspirin
- C. Carbon monoxide
- D. Cyanide
- E. Isopropyl alcohol

Answer: B Acetaminophen can cause a metabolic acidosis immediately after massive overdose or after hepatic failure develops. *N*-Acetylcysteine is the treatment, in addition to supportive care. Carbon monoxide and cyanide both inhibit oxidative phosphorylation and cause an elevated lactate level. Accepted treatments include hyperbaric oxygen therapy and hydroxocobalamin, respectively. Isopropanol does not cause a significant metabolic acidosis, and hemodialysis is rarely needed. Aspirin can uncouple oxidative phosphorylation and cause an anion gap metabolic acidosis; treatment for severe clinical effects of aspirin poisoning should include hemodialysis.

2. A middle-aged patient who is enrolled in a methadone-maintenance program presents to the emergency department with altered mental status. On physical examination, he is deeply obtunded and has a respiratory rate of 4/min with a pulse oximeter saturation reading of 85%. Which one of the following is the optimal initial approach?

- A. Bag-valve-mask ventilation
- B. Intubation and ventilation
- C. Irritant stimulation
- D. Naloxone, 2 mg IV
- E. Nasal cannula oxygen

Answer: A There is no rush to reverse the opioid intoxication with naloxone in patients who are in a health care setting because only oxygenation and ventilation are impaired by such an overdose. Simply externally supporting the patient's respiratory efforts with bag-valve-mask ventilation for a short time is sufficient while assessing the patient. Delivery of oxygen alone is not sufficient as it does not address the equally important ventilatory impairment. Naloxone may be used, but at a very low initial dose, such as 0.04 mg, to avoid intubation while also not precipitating opioid withdrawal, as can occur with larger doses. Endotracheal intubation is often required in patients with acute respiratory distress syndrome or who do not respond to naloxone.

3. A young woman with a history of depression presents to the emergency department after being started on a second psychiatric medication. Her initial vital signs include a body temperature of 108° F. After external cooling, what specific pharmacotherapy can be provided?

- A. Acetaminophen
- B. Cyproheptadine
- C. Dantrolene
- D. Diazepam
- E. Diphenhydramine

Answer: B Acetaminophen is ineffective for fever in which the body's set point is elevated. This patient likely has serotonin toxicity (or serotonin syndrome), which is due to excessive production of heat. Dantrolene is indicated for malignant hyperthermia and may have nonspecific effects in other hyperthermic syndromes. Diazepam is similarly nonspecific. Diphenhydramine is contraindicated because of its impairment of heat loss through sweating, given its antimuscarinic effects. Cyproheptadine is a serotonin receptor antagonist, and although it has not been adequately studied, in part given the rarity of serotonin toxicity, it is a specific therapy.

4. In a patient with an acute, intentional overdose with suicidal intent, which of the following laboratory tests is mandatory?
- A. Acetaminophen level
 - B. β -Human chorionic gonadotropin level
 - C. Aspirin level
 - D. Carbon monoxide (carboxyhemoglobin) level
 - E. Urine drug screen

Answer: A A pregnancy test is indicated in women of childbearing potential but not in other patients. Blood aspirin levels and urine drug screens are often obtained, but they offer little information in acute management. Aspirin poisoning should be identified clinically. Urine drug-of-abuse screens may help in a psychiatric evaluation but are as likely to mislead the initial clinical evaluation as they are to offer any insight. Carbon monoxide is a distinctly uncommon form of suicide and should be assessed by the history or other findings. Acetaminophen overdose is extremely common because of the wide availability of this medication in various forms, and it is very difficult to detect clinically until hepatic failure develops. Given the availability of an effective antidote, early detection is critical and should be sought in all patients with suicidal intent.

5. Which of the following methods of gastrointestinal decontamination should be performed in the majority of patients with oral exposures to poisons?
- A. Ipecac-induced emesis
 - B. No decontamination
 - C. Oral activated charcoal
 - D. Orogastric lavage
 - E. Whole bowel irrigation

Answer: B The benefit of gastrointestinal decontamination has been difficult to prove. For patients with high-risk exposures to significant quantities of toxin (such as calcium-channel blockers, monoamine oxidase inhibitors, colchicine), the benefits generally outweigh the risks. For the majority of exposures, it is perfectly acceptable to avoid oral decontamination, including administration of oral activated charcoal. Whole bowel irrigation is reserved for sustained-release medication (or drug mules), and orogastric lavage is generally performed only for the highest risk exposures in patients who present within several hours of ingestion. Ipecac is no longer used.

1. A 75-year-old woman was struck by a car going 20 miles per hour while she was crossing the street. The major impact was at the level of the knees, but she was thrown up onto the hood of the car before sliding onto the street. On arrival in the emergency department, she is alert with stable vital signs and a comfortable breathing pattern. She has obvious closed bilateral lower extremity fractures. Besides progressive edema in the fractured legs leading to compartment syndrome, what is the most likely trap to be anticipated when managing this patient?
- A. Delirium induced by pain medications
 - B. Immediate thromboembolic complications
 - C. Delayed presentation of visceral injury
 - D. Anoxia and seizures
 - E. Occult pneumothorax

Answer: C The primary survey will reveal the injuries to the lower extremities, but the secondary survey should include attention to possible abdominal injury. Failure to note a lacerated kidney could have disastrous consequences.

2. Three policemen in their early 30s are rushed to the emergency department after being injured by a vehicle-borne improvised explosive device. These victims are likely to suffer from all *except* which of the following?
- A. Overpressure injury to air-filled structures such as lung and bowel
 - B. Penetrating injury from flying debris
 - C. Blunt injury from impact with stationary objects
 - D. Crush injury from falling debris
 - E. Globe rupture from overpressure wave

Answer: E Overpressure waves affect air-filled structures such as the lung, bowel, and auditory system. Overpressure could affect hearing, as is seen in lightning injuries.

3. In the situation described in question 2, there are only two available operating rooms. The least injured of the three patients will have to wait 2 to 4 hours for surgery. During this time, an optimal resuscitation target is
- A. Systolic blood pressure of 140-160, intact sensorium, strong peripheral pulses, urine output of 4 mL/kg/hr, base deficit 0
 - B. Systolic blood pressure of 120-140, intact sensorium, strong peripheral pulses, urine output of 2 mL/kg/hr, base deficit 0-1
 - C. Systolic blood pressure of 100-120, intact sensorium, strong peripheral pulses, urine output of >1 mL/kg/hr, base deficit 0-1
 - D. Systolic blood pressure of 80-90, intact sensorium, palpable peripheral pulses, urine output of 0.5 mL/kg/hr, normalizing base deficit
 - E. Systolic blood pressure of 60-70, depressed sensorium, thready peripheral pulses, urine output of <0.5 mL/kg/hr, base deficit >5

Answer: D Recent research has shown that targeting lower systemic arterial pressure before exploratory surgery can lead to improved outcomes.

4. Typical of the hypermetabolic phase after severe burn or trauma are all of the following except which one?
- A. Hyperglycemia
 - B. Low systemic vascular resistance
 - C. Modest hypotension
 - D. Hyperlipidemia
 - E. Increased cardiac output

Answer: D A massive sympathetic discharge leads to hyperglycemia, low systemic vascular resistance, increased cardiac output, and modest hypotension, but an increase in lipids is not part of this picture.

Ch / 112 **ENVENOMATION**

1. Antivenom is most correctly described as which one of the following?

- A. A physiologic antidote that reverses the effects of venoms
- B. A mixture of antibodies that bind the toxins in a specific venom and can be associated with hypersensitivity reactions in humans
- C. Whole or fractionated immunoglobulin G (IgG) antibodies that reverse all the effects of envenomation.
- D. Specific toxins designed to neutralize the effects of venoms in humans
- E. IgG fractions that bind to a range of receptors to prevent the action of a specific venom

Answer: B Antivenom, which consists of a mixture of polyclonal antibodies raised against the toxins in a specific venom, binds to the venom components and thereby neutralizes venom in the circulation and prevents or reverses venom effects. Antivenom can be composed of whole immunoglobulins (IgG) or fractionated IgG, either F(ab')₂ or Fab. The administration of antivenom can result in hypersensitivity reactions because they contain foreign proteins.

2. Which of the following is the most appropriate treatment for North American rattlesnake envenomation?

- A. Early application of a pressure bandage and immobilization
- B. Immediate surgical decompression if the bite site is swollen and edematous
- C. Administration of antivenom for systemic and severe local effects and elevation of the bitten limb
- D. Universal early administration of antivenom with prophylactic antihistamines
- E. Administration of antivenom and fresh-frozen plasma to treat coagulopathy

Answer: C Definitive management of rattlesnake envenomation is antivenom plus elevation. Early surgical intervention has not been shown to be beneficial. Pressure bandaging is contraindicated in viper envenomation.

3. Which is the most correct statement about stingray injuries?

- A. Stingray injuries occur most commonly when they are stepped on in shallow water.
- B. Acute pulmonary edema is the major systemic effect of stingray envenomation.
- C. Antibiotics are never required for the treatment of stingray injuries.
- D. Most injuries occur from captive stingrays when tanks are cleaned.
- E. Immersion of the sting site in hot water for 20 minutes will provide complete relief from the pain.

Answer: A Stingray injuries occur most commonly when people tread on them in shallow water.

Stingray injuries cause severe local pain, bleeding, and a penetrating injury. Systemic effects are rare. Hot water may partially treat the pain, but pain usually recurs when the hot water is removed, unlike the pain from *Physalia* jellyfish stings, which usually resolves completely with hot-water immersion.

1. During the management of a patient who has multiple traumatic injuries, you note that a previously declining serum creatine kinase level now happens to rise. The patient's urine output is stable on aggressive hydration, and vital signs are normal. Which of the following represents the most likely clinical scenario accounting for the increasing creatine kinase?

- A. Infection
- B. Compartment syndrome
- C. Medication toxicity
- D. Underlying metabolic myopathy
- E. Acute respiratory failure

Answer: B In the management of the trauma patient with rhabdomyolysis, serum creatine kinase levels should steadily decline after a peak has been achieved, which typically is 3 to 5 days into effective treatment with aggressive fluid hydration. When the serum creatine kinase level increases, the clinician should suspect a compartment syndrome. Excessive pain is typically a clinical clue, but the use of regional anesthetic blocks or strong analgesics may mask the symptoms.

2. Rhabdomyolysis can be a complication of crush injury in people trapped at the site of a collapsed building. Which of the following field site interventions is most prudent to preserve both life and limb?

- A. Extremity hypothermia protocol
- B. Hypotensive resuscitation
- C. Aggressive fluid hydration
- D. Low-molecular-weight dextran to increase viscosity
- E. Extremity hyperthermia protocol

Answer: C Crush injury can cause both early and delayed deaths. The principal culprit for delayed morbidity and mortality is acute renal failure with associated metabolic complications. Early intravenous hydration, preferably within the first 6 hours, should aim to achieve a urine output in adults of 300 mL/hr to prevent acute renal failure.

3. Rhabdomyolysis can be a potentially life-threatening illness, with acute, subacute, and chronic complications, including compartment syndrome and acute kidney injury. Which of the following diagnostic tests is not necessary in the acute management of a significant case of rhabdomyolysis?

- A. Electrocardiogram
- B. Muscle biopsy
- C. Metabolic panel
- D. Urinalysis
- E. Measurement of creatine kinase levels

Answer: B In the management of rhabdomyolysis, the immediate focus is on treating metabolic complications and preventing kidney failure. Accordingly, a metabolic panel, measurement of creatine kinase levels, electrocardiogram, and urinalysis are all valuable assessments in detecting abnormalities and assisting in ongoing management. A muscle biopsy is not indicated in the acute management of the patient with rhabdomyolysis, but it can assist in determining whether a patient with recurrent rhabdomyolysis has an underlying inherited and acquired myopathy.

4. A serum creatine kinase level is commonly obtained to aid in both diagnosis and management of the patient with rhabdomyolysis. Which of the following characteristics are important to understand the baseline creatine kinase level in an individual patient?

- A. Sex
- B. Race
- C. Activity level
- D. A and B
- E. A, B, and C

Answer: E The difficulty in using serum creatine kinase levels alone to make the diagnosis of mild rhabdomyolysis partly lies in the wide variability of baseline levels. Men, African Americans, and more active people have higher baseline serum creatine kinase levels.

Ch / 114 **APPROACH TO THE PATIENT WITH RENAL DISEASE**

1. Idiopathic membranous nephropathy is associated with which of the following?

- A. Hepatitis B infection
- B. Hepatitis C infection
- C. Antibodies to the M-type phospholipase A2 receptor
- D. Nonsteroidal use
- E. None of the above

Answer: C Idiopathic membranous nephropathy has been identified to have antibodies to the M-type phospholipase A2 receptor. Although secondary membranous nephropathy can be associated with hepatitis B and rarely with hepatitis C or drugs, the idiopathic disease seems to be mediated by autoimmunity.

2. The most sensitive screening test for detection of a monoclonal gammopathy is

- A. Serum immunoelectrophoresis
- B. Serum free light chain ratio
- C. Urine for Bence Jones
- D. Bone marrow biopsy
- E. Urine free light chain ratio

Answer: B The serum immunoelectrophoresis is sensitive for the detection of intact immunoglobulins but less so for the detection of isolated light chains, which can occur in a substantial proportion of monoclonal gammopathies. An abnormal $\kappa:\lambda$ ratio is the most sensitive test to detect a clonal plasma cell disorder. Urine free light chain ratios are less reliable than serum ratios. A bone marrow biopsy is used to diagnose myeloma, but small numbers of plasma cells can cause many plasma cell disorders.

3. What is the best estimate of glomerular filtration rate in patients with renal function in the upper limits of the normal range?

- A. Modification of Diet in Renal Disease (MDRD) 1 equation
- B. Modification of Diet in Renal Disease (MDRD) 2 equation
- C. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
- D. None of the above

Answer: C MDRD 1 and 2 equations were derived in a population of patients with chronic kidney disease. MDRD 1 equation includes race, gender, creatinine, age, blood urea nitrogen, and albumin, but the other two equations do not include blood urea nitrogen or albumin. Of these equations, CKD-EPI is the most accurate for patients with mild chronic kidney disease.

4. Which of the following statements regarding the urine dipstick is false?

- A. The specific gravity can be lowered by contrast agents in the urine.
- B. Red blood cells, myoglobin, or hemoglobin can be detected by the presence of heme.
- C. The dipstick can miss Bence Jones proteins.
- D. The urine pH can be high in the presence of infections.
- E. The urine pH is usually higher than 5.5 in distal renal tubular acidosis.

Answer: A The high density of contrast material makes the urine specific gravity high rather than low. The dipstick detects all heme pigments, including myoglobin and hemoglobin, as well as red blood cells themselves. The dipstick detects albumin, but Bence Jones proteins may be missed or may cause only weak reaction in the dipstick. Hence, an immunoelectrophoresis or urine protein-to-creatinine ratio will be important; immunoelectrophoresis identifies the presence of clonal light chains, and the urine protein-to-creatinine ratio is for the actual quantification of the degree of proteinuria.

Ch / 117 POTASSIUM DISORDERS

1. A patient with vomiting develops hypokalemia from
 - A. Gastrointestinal potassium losses
 - B. Renal excretion of filtered bicarbonate in the steady state
 - C. Renal potassium wasting from early bicarbonaturia and hyperaldosteronism
 - D. Increased proximal tubule NaHCO_3 reabsorption
 - E. Distribution of potassium to the intracellular space

Answer: C Renal potassium wasting is the cause of severe potassium depletion in vomiting and plays a more important role than gastric losses because gastric fluid K^+ is low. Increased proximal tubule Na^+/H^+ exchanger increases NaHCO_3 reabsorption and maintains alkalosis but does not worsen K^+ losses. The alkaline urine and hyperaldosteronism favor the loss of K^+ with HCO_3^- .

2. Hypokalemic periodic paralysis can be associated with
 - A. Severe hypokalemia due to dietary ingestion of carbohydrates and subsequent insulin release
 - B. Hyperthyroidism
 - C. A mutation of a specific calcium channel responsible for cation current into muscle cells
 - D. Severe cardiac arrhythmias
 - E. All of the above

Answer: E Mutations of sodium or calcium channels that contribute to an inward leak of cations are the cause of a paradoxical depolarization of the sarcolemma membrane precipitated by stimuli that induce mild decreases in serum potassium. Symptoms may be precipitated by hypokalemic stimuli, such as carbohydrate loading. In some patients, especially Asians, it is associated with thyrotoxicosis. In occasional cases, severe hypokalemia can cause cardiac arrhythmias.

Ch / 118 ACID-BASE DISORDERS

1. A patient with type 1 diabetes mellitus, on hemodialysis, underwent a deceased donor combined renal-pancreas organ transplantation. The pancreatic duct was drained through the recipient's urinary bladder. The function of the transplanted kidney and pancreas was excellent. Which of the following compensations would occur for the post-transplantation acid-base disorder?
 - A. Respiratory hypoventilation
 - B. Respiratory hyperventilation and increased renal ammoniogenesis
 - C. Metabolic alkalosis due to the severe urinary potassium wasting
 - D. Renal chloride losses to match pancreatic bicarbonate loss
 - E. Initial HCO_3^- losses followed by paradoxical aciduria

Answer: B The patient would lose pancreatic NaHCO_3 in the bladder, thereby causing a severe hyperchloremic acidosis, which would be compensated by hyperventilation and increased renal attempts to excrete the acid load by increasing ammonia production in the newly functional kidney.

2. A 36-year-old woman returns from an overseas trip with profuse watery diarrhea and is found to have a urinary Na^+ of 34 mEq/L, a urinary K^+ of 41 mEq/L, and a urinary Cl^- of 6 mEq/L. Which one of the following statements is most likely to be correct?
 - A. She has severe metabolic acidosis from the diarrhea.
 - B. She has both metabolic acidosis from diarrhea and bicarbonaturia from an unsuspected renal tubular acidosis.
 - C. She is acidemic from the diarrhea but must also have been vomiting.
 - D. She has not been vomiting but has metabolic alkalosis and alkalemia.
 - E. Her urinary NH_4^+ must be very high.

Answer: D She has chloride-wasting secretory diarrhea, which has caused hypochloremic metabolic alkalosis. There is bicarbonaturia from the net gain of plasma bicarbonate, and that is why her urinary Na^+ and K^+ are high. She is conserving chloride. If she was acidemic with a mixed hypochloremic alkalosis from vomiting and an acidosis from diarrhea, the net Cl^- in the blood would be high and her urinary anion gap would be less than 0 ($\text{Na}^+ + \text{K}^+ - \text{Cl}^- < 0$). There is no evidence that urinary NH_4^+ is high, and the positive urinary anion gap is normally seen in hypochloremic alkalosis. It does not imply a renal tubular acidosis. The teaching point is that not all diarrhea causes metabolic acidosis, and diarrhea may cause metabolic alkalosis if the stool has high Cl^- .

Ch / 119

DISORDERS OF MAGNESIUM AND PHOSPHORUS

1. A 55-year-old woman with ovarian cancer is being treated with carboplatin, Taxol, and pelvic irradiation. She now complains of chronic diarrhea and is found to have the following blood serum levels: magnesium 0.8 mg/dL, calcium 6.1 mg/dL, albumin 3 g/dL, and creatinine 1.3 mg/dL. Her urine magnesium is 17 mg/dL, with a urine creatinine 58 mg/dL. The most likely cause of her laboratory abnormalities is:

- A. Carboplatin.
- B. Diarrhea.
- C. Vitamin D deficiency.
- D. Radiation nephritis.
- E. Primary hypoparathyroidism.

Answer: A The fractional excretion of magnesium is 68%, thereby indicating that the cause of the hypomagnesemia is severe renal magnesium wasting rather than diarrheal losses. Platinum-based chemotherapeutic agents, which are toxic to the renal tubule, are a well-recognized cause of hypomagnesemia. This toxicity, which is more common with cisplatin but also has been reported with carboplatin, can persist after discontinuation of therapy. The hypocalcemia in this case is likely secondary to the severe hypomagnesemia, which impairs parathyroid hormone secretion and also causes peripheral resistance to its actions.

2. A 46-year-old man with diabetes mellitus, chronic stage IV kidney disease, and chronic constipation has been taking magnesium citrate for 4 consecutive days. He now presents with hypotension, muscle weakness, and hyporeflexia. His serum magnesium level is 5.8 mg/dL and his serum creatinine 3.6 mg/dL. All of the following treatments would be appropriate *except*:

- A. Forced diuresis with saline and furosemide.
- B. Hemodialysis.
- C. Calcium chloride intravenously.
- D. Sodium polystyrene sulphonate.
- E. Lactulose

Answer: D Magnesium ingestion in patients with renal insufficiency can cause hypermagnesemia. Hypotension, flaccid muscle paralysis, and hyporeflexia are typical manifestations. Hypermagnesemia can be treated by antagonizing the effects of magnesium with intravenous calcium salts, by increasing the excretion of magnesium with furosemide, or by hemodialysis. Alternative laxatives that are safe to use with impaired renal function include lactulose, docusate, bisacodyl, and senokot. Sodium polystyrene sulfonate is effective at binding intestinal potassium but not magnesium; if administered in this setting, it could cause hypokalemia that would exacerbate the muscle weakness.

3. An 18-year-old woman with anorexia nervosa and malnutrition was admitted for parenteral nutrition and subsequently developed hypophosphatemia with a serum phosphorus level of 0.6 mg/dL. The mechanism for hypophosphatemia is:

- A. Renal phosphate wasting.
- B. Fanconi syndrome.
- C. Shift of phosphorus into intracellular stores.
- D. Diarrheal phosphate losses.
- E. Excess bone deposition.

Answer: C In malnourished patients, total body phosphate stores are depleted. Intravenous refeeding without appropriate phosphate supplementation with carbohydrate-rich fluids may stimulate insulin release and cause an acute shift of phosphate into intracellular stores.

4. A 55-year-old man with HIV infection is maintained on antiretroviral therapy with tenofovir, emtricitabine, ritonavir, and atazanavir. Routine laboratory examination revealed the following: serum sodium 133 mEq/L, potassium 2.6 mEq/L, chloride 110 mEq/L, bicarbonate 15 mEq/L, glucose 96 mg/dL, urea nitrogen 16 mg/dL, creatinine 1.8 mg/dL, phosphorus 0.7 mg/dL, and uric acid 2.6 mg/dL. Urinalysis shows 4+ glucose and trace protein. The most likely cause of his hypophosphatemia is:

- A. HIV-associated nephropathy.
- B. Tenofovir.
- C. Acute tubular necrosis.
- D. Multiple myeloma.
- E. Oncogenic osteomalacia.

Answer: B This patient has hypophosphatemia, hypokalemia, a probable hyperchloremic metabolic acidosis, hypouricemia, and glycosuria without hyperglycemia. All of these findings are features of Fanconi syndrome or proximal tubulopathy. Tenofovir is an acyclic nucleotide analogue reverse-transcriptase inhibitor (as are cidofovir and adefovir) that is transported into the proximal renal tubule by organic anion transporters and causes mitochondrial toxicity. Fanconi syndrome occurs in as many as 20% of tenofovir-treated patients. Tenofovir also can cause acute tubular necrosis and acute kidney injury, but these clinical syndromes would tend to increase the serum phosphate concentration. Multiple myeloma can also cause Fanconi syndrome, but it is much less common. Oncogenic osteomalacia is a rare syndrome caused by mesenchymal tumors that secrete circulating phosphaturic factors, which cause renal phosphate wasting; however, oncogenic osteomalacia is not associated with Fanconi syndrome.

5. A 34-year-old man presents with muscle soreness and voiding dark brown urine soon after initiating a high-intensity home exercise regimen. His serum potassium is 6.5 mEq/L, creatinine 4.6 mg/dL, phosphorus 8.3 mg/dL, and creatine kinase 17,500 U/L. The most appropriate treatment for his hyperphosphatemia is:

- A. Calcium acetate.
- B. Calcium carbonate.
- C. Insulin and glucose.
- D. Sodium bicarbonate.
- E. Hemodialysis.

Answer: E This patient has rhabdomyolysis, as evidenced by the very high creatine kinase value. Hyperkalemia and hyperphosphatemia resulting from release of intracellular ions is typical in this disease. Myoglobinuria is thought to be the cause of acute kidney injury. Given the degree of renal insufficiency and concomitant hyperkalemia, extracorporeal therapy with either hemodialysis or continuous venovenous hemodiafiltration would be appropriate and would effectively remove phosphate. Forced saline or alkaline diuresis is contraindicated in the setting of renal insufficiency. Calcium salts would not be very effective because they would bind only dietary phosphate in the

intestinal lumen; moreover, some of the calcium would be absorbed and increase the likelihood of metastatic precipitation of calcium-phosphate crystals. Insulin would shift some phosphorus into cells, but this would not have a large or lasting effect. Sodium bicarbonate can be used in an attempt to alkalinize the urine, which is believed to decrease the renal toxicity of myoglobin, but it would not affect the phosphate level.

Ch / 120 ACUTE KIDNEY INJURY

1. Acute kidney injury is a common disorder in hospitalized patients, occurring in up to 20% of all adult admissions. Within a broad differential, which particular process is most likely as the cause of acute kidney injury in hospitalized patients?

- A. Outflow obstruction
- B. Glomerulonephritis
- C. Acute interstitial nephritis
- D. Prerenal azotemia
- E. Ischemic acute tubular necrosis

Answer: D Up to 50% of patients diagnosed with acute kidney injury in a hospital setting have prerenal azotemia. It is important to make this diagnosis, and it usually is a rapidly reversible alteration that is responsive to fluid therapy, with low morbidity and mortality if treated rapidly and appropriately. However, prerenal azotemia also can lead to ischemic acute tubular necrosis if it persists or worsens.

2. The diagnosis of prerenal azotemia is made after an appropriate history and physical examination. What urinary and serum biomarkers can be used to help confirm the diagnosis of prerenal azotemia?

- A. A ratio of BUN to creatinine greater than 20
- B. A fractional excretion of sodium less than 1%
- C. A bland urine analysis
- D. A and B
- E. All of the above

Answer: E Prerenal azotemia is an adaptation by the kidney to hypoperfusion without cellular injury. In the prerenal state, the kidney is being inadequately perfused but not yet to a level that results in low cellular ATP and cell injury. The kidney tries to increase the volume status of the patient by reabsorbing nearly all of the filtered sodium, thereby resulting in a low FENa. Urea reabsorption is also increased, thereby resulting in the high ratio of BUN to creatinine.

3. Risk factors for the development of acute kidney injury include all of the following *except*?

- A. Chronic kidney disease
- B. Volume depletion
- C. Use of nonsteroidal anti-inflammatory agents
- D. Hypertension with blood pressure of 160/100 mm Hg
- E. Nephrotoxins

Answer: D Hypertension causes chronic kidney injury but does not usually cause acute kidney injury except with malignant hypertension. Of the remaining four risk factors, chronic kidney disease is the most important; the more severe the chronic kidney disease, the more likely acute kidney injury is to occur.

4. Serum creatinine is used as a marker of glomerular filtration and therefore kidney function in patients. Numerous attempts have been made to develop estimating equations based around serum creatinine and other serum markers in an attempt to help quantify glomerular filtration rate without undertaking timely and costly studies. In a patient with acute kidney injury and either a rising or falling serum creatinine, the calculation of an eGFR is inappropriate for which of the following reasons?
- A. Serum creatinine is not in equilibrium and therefore it is not possible to calculate eGFR.
 - B. There may be an alteration in the rate of creatinine released from muscles in a hospitalized patient.
 - C. Other factors such as fever, glucocorticoids, or trauma, influence creatinine release.
 - D. With complete loss of kidney function, the serum creatinine can rise between 1 and 4 mg/dL/day depending on the patient's circumstances.
 - E. All of the above

Answer: E Although a stable serum creatinine can be used to estimate the glomerular filtration rate using estimating equations, the equations are reasonably accurate only when the serum creatinine level is stable. Multiple factors, including fever, glucocorticoids, or trauma, affect the muscle release of creatine, which is the precursor of serum creatinine.

5. Dialysis for acute kidney injury is a sign of moderate-to-severe injury with an enhanced morbidity and mortality for the patient. Which of the following is true regarding dialysis for acute kidney injury?
- A. Dialysis should be intensive both in frequency and duration to provide the patient with the most appropriate internal milieu.
 - B. The major reasons to start dialysis in a patient with acute kidney injury include acidosis, hyperkalemia, and volume overload.
 - C. Continuous renal replacement has been shown to have a better outcome for patients than intermittent hemodialysis.
 - D. The serum creatinine level at the initiation of dialysis inversely correlates with outcomes in patients with acute kidney injury.
 - E. Starting dialysis early in patients with sepsis improves outcomes.

Answer: B The patient's volume, potassium level, and acid-base status are major indications for dialysis in AKI. Adequate dialysis is critically important, but neither increasing the intensity of dialysis nor initiating it earlier improves outcomes.

1. A 24-year-old Asian man presents to his family physician with one episode of painless gross hematuria. He is otherwise healthy with no significant family history. On physical examination, his blood pressure is normal and there are no other abnormalities. Laboratory examination shows a normal metabolic profile, hemogram, liver enzymes, and renal function tests, as well as a negative urine culture. Serologic tests including complement levels, antinuclear antibody, antineutrophil cytoplasmic antibody, and a hepatitis panel are all negative. Urine examinations show 3+ blood, 3+ protein, and many RBCs and RBC casts on microscopic examination. His renal ultrasound is normal. A repeat physical examination and laboratory tests after 1 week show 1+ heme, 5 to 10 RBCs, and trace urinary protein, which quantitates to 150 mg/day. Your recommendation at this point should be:

- A. Continue observation.
- B. Renal biopsy.
- C. Empiric therapy with alternate day steroids.
- D. Genetic testing for patient and his family.
- E. Urology referral.

Answer: A The presence of gross hematuria associated with RBC and RBC casts and proteinuria point to a glomerular origin as opposed to a urologic origin (hence a urologic consult is not appropriate). In this patient with an Asian ancestry, negative serologies (particularly normal complement levels), and a self-limiting course, an IgA nephropathy is the most likely diagnosis. A renal biopsy is not appropriate at this time because he has no high-risk features for progressive disease, such as proteinuria greater than 1 g/day or impaired renal function. Likewise, empiric treatment is not warranted with these low-risk features. Although hereditary nephritis may present like this, an insidious progression to renal failure without episodes of gross hematuria is more typical, and the absence of a family history makes this entity less likely.

Wyatt RJ, Julian BA. IgA nephropathy. *N Engl J Med*. 2013;368: 2402-2414.

2. A 50-year-old man is admitted with shortness of breath, 1 week of hemoptysis, and mild swelling of his lower extremities. He also notes a 1-month history of myalgia and arthralgia, partially relieved by ibuprofen, which he takes twice daily. On examination, his blood pressure is 150/90 mm Hg, he is afebrile, and his lung examination shows bibasilar crackles. Laboratory tests reveal mild leukocytosis with a neutrophilic preponderance and hemoglobin of 11.2 g/dL. His urine shows 2+ protein, many RBCs, and a few RBC casts. His creatinine is 2.4 mg/dL. His chest radiograph is notable for bilateral diffuse infiltrates, which worsen in the next 24 hours. Serologic tests are pending. Your management at this point would include:

- A. Continue observation until serologic tests are available
- B. Arrange for an urgent renal biopsy
- C. Choice B + intravenous steroids
- D. Choice B + intravenous steroids + plasmapheresis

Answer: D This patient has the pulmonary renal syndrome with a nephritic urine sediment. The possibilities are immune complex disease, anti-GBM antibody disease (Goodpasture syndrome), and small vessel vasculitis. The hemoptysis and worsening pulmonary infiltrate require empirical therapy with high-dose steroids and plasmapheresis while awaiting renal biopsy and serologic results to confirm the diagnosis. Plasmapheresis is indicated in view of the pulmonary hemorrhage. Cyclophosphamide (or rituximab in small vessel vasculitis) is administered after confirming the diagnosis.

Bolton WK. Pulmonary renal syndrome and emergency therapy. *Contrib Nephrol*. 2010;165:166-173. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis.

Klemmer PJ, Chalermkulrat W, Reif MS, et al. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. *Am J Kidney Dis*. 2003;42:1149-1153.

3. A 65-year-old white woman with nephrotic syndrome (urine protein 6 g/ day, normal renal function, serum albumin 2.2 g/dL) recently has been diagnosed with membranous nephropathy. All of the following statements about membranous nephropathy are true *except*:

- A. Further investigations should include a malignancy workup.
- B. The patient should start on cyclic cyclophosphamide alternating with steroids.
- C. There is a significant risk for thrombotic events, and prophylactic anticoagulation may be considered in patients at low risk for bleeding.
- D. She should be screened for hepatitis B, which is known to be associated with membranous nephropathy.
- E. She is at risk for progressive renal disease if proteinuria remains at the same level after 6 months.

Answer: B Patients with membranous nephropathy should be evaluated for secondary causes, including malignancies, infections (e.g., hepatitis viruses), systemic lupus, and medications. The risk for thrombotic events is significant and rises when the serum albumin level is less than 2.8 g/dL; some authorities recommend prophylactic anticoagulation in such patients if they are at low risk for bleeding. The risk for progressive renal disease is associated with persistent high-grade proteinuria. However, approximately 30% of patients undergo spontaneous remission, so observation for 3 to 6 months is recommended before considering specific immunosuppression.

Waldman M, Austin HA, 3rd. Treatment of idiopathic membranous nephropathy. *J Am Soc Nephrol.* 2012;23:1617-1630.

4. A 71-year-old man with controlled hypertension has been experiencing progressive shortness of breath and lower extremity edema for 1 month. He has just been discharged after being admitted with a diagnosis of heart failure with preserved ejection fraction. On examination, his blood pressure is 110/70 mm Hg supine but drops to 90/60 mm Hg on standing with no increase in his heart rate. His liver is enlarged 5 cm below the costal margin. His lung examination shows diminished breath sounds over the bases. Diagnostic tests done during his hospitalization show a normal hemogram, a serum albumin 2.5 g/dL, serum creatinine 1.5 mg/dL, and urine protein 8 g/day with no cells in the urine sediment. Further diagnostic evaluation shows normal serologies (including complement levels), an elevated λ light chain, and a decreased κ/λ ratio. A renal biopsy shows mesangial expansion with an amorphous material on light microscopy. All of the following statements are true about this patient's disease, *except*:

- A. The mesangial deposits are Congo red positive with 10-nm fibrils on electron microscopy.
- B. Treatment directed against the abnormal plasma cell clone may help stabilize his disease course.
- C. Bone marrow biopsy typically will not show features of multiple myeloma.
- D. There is usually an underlying inflammatory condition as the basis of this disease.
- E. Fat pad biopsy may obviate the need for a renal biopsy.

Answer: D This patient with nephrotic-range proteinuria, cardiac failure with preserved ejection fraction, and autonomic neuropathy likely has AL amyloid, which on biopsy (renal, cardiac, fat pad, or gingival) will show the typical deposits that stain apple green on Congo red staining under a polarizing microscope. Treatment is similar to that for myeloma even though the bone marrow does not show evidence for myeloma. The elevated λ light-chain levels are a clue for AL amyloid; definitive diagnosis is based on staining the biopsy material for light chains, which will show the monoclonal nature of the deposit. The diagnosis of AA amyloid is made when the Congo red stain shows the typical birefringence but the deposits stain for AA protein.

Desport E, Bridoux F, Sirac C, et al. AL amyloidosis. *Orphanet J Rare Dis.* 2012;7:54.

1. A 35-year-old man employed in a long-term modeling contract sees you for the first time. He is worrying that he had seen blood in his urine. An ardent disciple of exercise, dieting, and supplements, he is in a monogamous relationship and taking no pharmaceuticals. On routine testing he has a serum creatinine of 2.3 mg/dL with +2 protein and blood in his urine without bacteria. Computed tomographic scan revealed normal-sized kidneys and a bladder mass. The most likely cause of his renal injury is:

- A. Herbal nephropathy
- B. BK virus nephropathy
- C. Myeloma kidney
- D. Sjögren syndrome
- E. Silent pyelonephritis

Answer: A Patient was taking various unknown herbal agents freely available over the counter. The likely exposure to aristolochic acid in these supplements has led to chronic interstitial nephritis and a uroepithelial tumor in the bladder producing hematuria. BK virus nephropathy is seen only after transplantation on immunosuppression. This is the wrong age for myeloma kidney, there are no symptoms of Sjögren syndrome, and pyelonephritis is unlikely in the absence of fever and bacteria in the urine.

2. A 44-year-old female office manager for a well-known U.S. senator has suffered from self-described stomach pains for many years. In the distant past, she was periodically given short courses of tetracycline from a friend for presumed gastric ulcers with unclear relief. Her regular physician has had her on long-term proton pump inhibitors for chronic gastroesophageal reflux. Following a persistent low-grade fever, she visited her physician, and testing revealed a recent rise in her serum creatinine to 1.5 mg/dL, pyuria without bacteria, and a fever of 100.5° F. The most likely diagnosis is:

- A. Omeprazole nephropathy
- B. Sarcoidosis
- C. Tetracycline nephropathy
- D. Malakoplakia
- E. Renal calculi

Answer: A Patient was taking proton pump inhibitors for a long time, which can cause acute interstitial nephritis; the reaction is idiosyncratic. Tetracyclines are an unlikely cause because she is not taking them presently. She has no symptoms of sarcoidosis. Malakoplakia is extremely rare and typically involves the lower urinary tract. Renal calculi often produce hematuria, a different pain syndrome, and raise serum creatinine usually as a result of bilateral obstruction.

3. A 67-year-old retired auto mechanic living in a rural town visits his physician with complaints of fatigue, shortness of breath, and generally not feeling well. He takes no pharmaceuticals or over-the-counter drugs. His vital signs were normal, HIV screen was negative, serum calcium was 11.9 mg/dL, serum hemoglobin was 7.9 g/dL, and serum creatinine was 2.8 mg/dL. His urine protein was 723 mg/L, and only a few white blood cells were found on urinalysis. He was admitted to the hospital when a lucency on his left femur was seen on a bone radiograph. The most likely diagnosis is:

- A. Myeloma nephropathy
- B. Focal glomerulosclerosis
- C. Xanthogranulomatous pyelonephritis
- D. Balkan nephropathy
- E. Ouch-Ouch disease

Answer: A The patient presents with substantial clinical evidence of classic plasma cell dyscrasia, probably a form of myeloma. His urine contained highly abnormal levels of κ light chains with a monoclonal spike. Biopsy revealed cast nephropathy with diffuse interstitial nephritis, and his elevated calcium with lytic lesions suggests systemic bony involvement. With normal vital signs, less

than a gram of protein in the urine, and a negative HIV test, focal glomerulosclerosis seems unlikely. The absence of fever or obvious pyuria eliminates xanthogranulomatous pyelonephritis. Patients with Balkan nephropathy or Ouch-Ouch disease (cadmium toxicity) do not normally present with hypercalcemia and lytic bone lesions, and there is no history of exposure to herbals or toxic metals.

4. A 19-year-old female college student appeared in a student health clinic with complaints of generalized weakness, a sense of increased respiration, and bilateral blurry vision. She was taking birth control pills but had been otherwise well. Her college physical examination was completely normal, and her childhood uneventful. Her vital signs were normal, and her retina was normal on ophthalmoscopy. Her blood work showed a serum creatinine of 1.6 mg/dL, serum HCO₃ of 19 mEq/L, serum glucose of 90 mg/dL, serum calcium of 9.1 mg/dL, and a serum phosphate of 3.2 mg/dL. Her chest radiograph was normal, but her urinalysis demonstrated pyuria and glycosuria. She was admitted urgently for a kidney biopsy and a formal ophthalmologic examination. The most likely cause is:

- A. Tubulointerstitial nephritis and uveitis (TINU) syndrome
- B. Sarcoidosis
- C. Epstein-Barr virus nephropathy
- D. Lead nephropathy
- E. Light chain nephropathy

Answer: A The patient presents with substantial clinical evidence of Fanconi syndrome with an elevated serum creatinine level. Her kidney biopsy will likely show interstitial nephritis, and her eye examination will likely reveal anterior uveitis. Sarcoidosis is unlikely with a normal chest radiograph and serum calcium level. She has no findings of Epstein-Barr virus infection, no history of lead exposure, and is too young for light chain disease.

1. A 64-year-old Hispanic man with moderately controlled type 2 diabetes, hypertension, and chronic kidney disease with nephrotic-range proteinuria and serum creatinine of 2.4 is admitted to the hospital because he has had a stroke. Which is the best single answer concerning this patient?
 - A. Intensive glycemic control of type 2 diabetes does not decrease the incidence of nephropathy or cardiovascular mortality
 - B. Patients with type 2 diabetes with chronic kidney disease always have increased albuminuria.
 - C. In type 2 diabetes, proteinuria correlates with an increased incidence of coronary heart disease but not with stroke.
 - D. In both type 1 and type 2 diabetes, hypertension usually indicates evidence of diabetic nephropathy
 - E. Nephrotic-range proteinuria is greater than 1.5 g/day of proteinuria.

Answer: A Intensive glycemic control of type 2 diabetes does not decrease the incidence of nephropathy and cardiovascular mortality. The ACCORD trial indicated an increased risk of overall mortality with intensive glucose lowering in this population. Recent meta-analyses have indicated a decrease in cardiovascular disease outcomes, specifically nonfatal myocardial infarctions and risk of progression of nephropathy, but could not confirm that there was any decrease in the incidence of nephropathy or cardiovascular mortality. B is false because about 20% of type 2 diabetic patients with chronic kidney disease do not have albuminuria. C is false because proteinuria correlates with an increased incidence of coronary heart disease and stroke in patients with type 2 diabetes. D is false because patients with type 2 diabetes are older and often have hypertension before the onset of diabetic kidney injury. E is false because the definition of nephrotic range proteinuria is greater than 2.5 g/day.

2. Which is the best single answer concerning structural changes to the kidney during the course of diabetic nephropathy?
 - A. Afferent and efferent arteriolar hyalinosis are nonspecific findings and are found in a variety of glomerular diseases.
 - B. More than 90% of patients with type 2 diabetes have evidence of retinopathy at the time of diagnosis of overt nephropathy.
 - C. Thickening of the glomerular basement membrane is a late finding in diabetic nephropathy.
 - D. Kimmelstiel-Wilson lesions are observed in a minority of patients diagnosed with diabetic nephropathy.
 - E. Kidney hypertrophy always indicates that the patient will develop overt nephropathy.

Answer: D Kimmelstiel-Wilson lesions are observed in a minority of patients diagnosed with diabetic nephropathy. A is false because the combination of afferent and efferent arteriolar hyalinosis is characteristic of diabetic nephropathy. B is false because only 60% to 65% of type 2 diabetic patients have retinopathy concomitant with onset of nephropathy. C is false because thickening of the glomerular basement membrane can be observed 2 to 5 years after the onset of diabetes and occurs before the onset of overt proteinuria or decline in renal function. E is false because kidney hypertrophy does not always indicate that the patient will develop overt nephropathy.

1. You are asked to review a case regarding a 67-year-old man who is being evaluated for progressive chest pain. He has type 2 diabetes mellitus with chronic kidney disease ($\text{HbA}_{1c} = 8.7\%$, serum Cr = 2.1 mg/dL). Other tests include ratio of total cholesterol to high-density lipoprotein of 7.2 and a distant history of smoking (15 pack years), but he quit 20 years ago. He is also noted to have poorly controlled hypertension and despite being treated with atenolol, hydrochlorothiazide, and amlodipine, with systolic pressures remaining above 180 mm Hg. He states that he is compliant with all medications but does not follow his diet very well. His ejection fraction by echocardiography is 40%, and stress echocardiography showed stress-induced anterior wall motion abnormalities. What should you recommend?
 - A. A gadolinium-enhanced renal artery magnetic resonance image after overnight hydration with 0.5% normal saline. If it is positive for renal artery stenosis, perform renal angiography at the time of the cardiac catheterization that he also needs.
 - B. Proceed with a cardiac catheterization after overnight hydration. Perform renal angiography only if the patient will require coronary bypass surgery. If coronary stenting is performed, delay the renal angiography for 6 weeks to reduce his acute exposure to contrast dye.
 - C. Start statin therapy and improve his diabetes management. When his cardiac evaluation is completed, consider initiating an ACE inhibitor if his renal function remains stable and careful follow-up of the serum creatinine concentration.
 - D. Order renal artery Doppler studies with resistive indices. If there is greater than 60% stenosis of one or both renal arteries and the resistive index is less than 0.8, proceed with renal artery stenting of the most severe lesion and stage the second artery if necessary.
 - E. None of the above

Answer: C The patient is taking multiple hypertensive medications, but his blood pressure remains poorly controlled, and he has renal dysfunction, left ventricular dysfunction, and probable coronary artery disease. Therefore, he has many risk factors for atherosclerotic renal artery stenosis. Multiple randomized trials have shown no efficacy for renal revascularization for atherosclerotic renal artery stenosis, so screening in this scenario would be of no clinical benefit. Furthermore, his estimated glomerular filtration rate is likely to be less than 30 mL/min, thereby making gadolinium contraindicated. On the other hand, treatment of his risk factors and addition of an ACE inhibitor for left ventricular dysfunction and diabetes mellitus has the most clinical benefit for reducing major adverse cardiovascular events.

1. In confirming a diagnosis of autosomal dominant polycystic kidney disease in an adult patient with a positive family history, which of the following is needed?

- A. Ultrasonography
- B. Gene mutational analysis of the patient
- C. Gene mutational analysis of the patient and at least two family members (one of whom has the disease)
- D. MRI to determine total cyst volume
- E. All of the above

Answer: A A positive ultrasonography result in a patient with a positive family history of autosomal dominant polycystic kidney disease is sufficient to confirm the diagnosis. Unfortunately, a negative ultrasound result does not necessarily exclude the disease in such a patient.

2. Risk factors for disease progression in autosomal dominant polycystic kidney disease include

- A. male gender.
- B. early onset of hypertension.
- C. proteinuria.
- D. height-adjusted total kidney volume greater than 600 cc/m
- E. all the above.

Answer: E Male gender, early onset of hypertension, total kidney volume greater than 600 cc/m, and proteinuria are risk factors for the progression of disease.

1. A 50-year-old man presents with lower urinary tract symptoms. Digital rectal examination reveals an enlarged prostate complicated by lower urinary tract symptoms. In discussing the potential side effects of dutasteride with the patient, which of the following would *not* apply in regard to sexual function?

- A. Decreased libido
- B. Decreased ejaculatory volume
- C. Erectile dysfunction
- D. Ejaculatory pain
- E. A and C

Answer: D 5 α -Reductase inhibitors, such as dutasteride, were developed to block the conversion of testosterone to dihydrotestosterone, thus reducing prostate volume and thereby decreasing bladder outlet obstruction. The side effects of a 5 α -reductase inhibitor include decreased libido, decreased ejaculatory volume, and erectile dysfunction.

2. A 60-year-old man has significant lower urinary tract symptoms refractory to other therapies. He does not have any major morbid conditions that would be contraindications to surgery. Which of the following is not an absolute indication for surgery?

- A. The patient has developed acute urinary retention.
- B. The patient has renal insufficiency secondary to benign prostatic hyperplasia.
- C. The patient has recurrent gross hematuria due to benign prostatic hyperplasia.
- D. Cystoscopy revealed a bladder diverticulum.
- E. B and D

Answer: D Surgical intervention is an appropriate treatment alternative for patients with moderate to severe lower urinary tract symptoms and for patients who have developed acute urinary retention or other benign prostatic hyperplasia-related complications. Surgery is recommended for patients who have renal insufficiency secondary to benign prostatic hyperplasia; for patients who have recurrent urinary tract infections, bladder stones, or gross hematuria due to benign prostatic hyperplasia; and for those who have lower urinary tract symptoms refractory to other therapies. The presence of a bladder diverticulum is not an absolute indication for surgery unless it is associated with recurrent urinary tract infection or progressive bladder dysfunction.

3. A 35-year-old man presents with the following symptoms indicative of chronic prostatitis/chronic pelvic pain syndrome: frequent urination, increased urgency, and post-ejaculatory pain for the past 4 months. In this case, which of the following evaluations would not be mandatory?

- A. Abdominal examination
- B. Digital rectal examination
- C. Semen analysis
- D. Urinalysis
- E. Urine culture

Answer: C The physician must ask pertinent questions about voiding history, sexual history, characterization of symptoms, and pain. A thorough medical and surgical history should focus on neurologic disorders and pelvic surgery. Physical examination must include abdominal, external genital, perineal, and digital rectal examination. Attention should be placed on identifying pelvic wall discomfort, structural abnormalities, or prostatic pain on digital rectal examination. Urinalysis and urine culture should be performed for every patient.

4. A 45-year-old man has a history of recurrent urinary tract infections. Bacterial growth on culture of expressed prostatic fluid and a post-prostate massage urine specimen confirms a diagnosis of chronic bacterial prostatitis. The expressed prostatic secretion contains more than 10 white blood cells per high-power field. Digital rectal examination demonstrates a normal benign prostate. Which antibiotic class is usually recommended for treatment of his prostatitis?

- A. Fluoroquinolones
- B. Macrolides
- C. Trimethoprim/sulfamethoxazole
- D. Doxycycline
- E. None of the above

Answer: A Fluoroquinolones have been recommended as first-line therapy for chronic bacterial prostatitis. With high lipid solubility, they show the best penetration into the prostate and seminal fluid. The usual course is 4 to 6 weeks.

5. After 48 hours of therapy with appropriate intravenous broad-spectrum antibiotics for his prostatitis, a 40-year-old man continues to be febrile and highly symptomatic with chills and malaise. Which of the following is the “gold standard” imaging modality for a patient with a suspected prostatic abscess?

- A. Computed tomography scan
- B. Magnetic resonance imaging scan
- C. Abdominal plain film and intravenous pyelography
- D. Transrectal ultrasound
- E. There is no gold standard imaging modality for a patient with a suspected prostatic abscess.

Answer: D Transrectal ultrasound is a useful tool in identifying a prostatic abscess and is considered the gold standard. This modality can also identify seminal vesicle or ejaculatory duct abnormalities, especially in patients with ejaculatory pain or hematospermia.

1. A 65-year-old African American patient with stage 4 chronic kidney disease (CKD; estimated glomerular filtration rate, 20 mL/minute) is examined in your office. Among laboratory abnormalities uncovered, the subject's serum phosphorus level is 5.6 mg/dL. Regarding the increase in serum phosphorus, which of the following options is correct?

- A. An increase in serum phosphorus has not been associated with adverse outcomes in nondialysis patients with CKD and it can be ignored.
- B. Use of phosphate binders in nondialysis CKD patients has been shown to correct the high serum phosphorus level and should be encouraged.
- C. The patient should meet with a nutritionist for counseling in methods that control phosphate intake. The dietitian's help is needed because phosphates have been added to many foods, and patients must learn how to avoid foods rich in phosphates and how to use phosphate binders.
- D. The parathyroid hormone and fibroblast growth factor 23 (FGF23) levels should be measured as they could be subnormal.

Answer: C An increase in serum phosphorus is a strong predictor of mortality and adverse outcomes in CKD patients. Because phosphates are added to prepared foods, it is difficult to reduce dietary sources of phosphates. However, clinical trials of reducing serum phosphorus by giving phosphate binders to predialysis CKD patients have not demonstrated improved mortality.¹ Both FGF23 and parathyroid hormone increase urinary losses of phosphates, so they rise when serum phosphorus levels rise.

1. Chue CD, Townend JN, Moody WE, et al. Cardiovascular effects of sevelamer in stage 3 CKD. *J Am Soc Nephrol*. 2013;24:842-852.

2. Which one of the following statements about the interplay of diet and treatment for CKD patients is true?

- A. High-salt diets interfere with angiotensin-converting enzyme (ACE) inhibitor therapy, thereby compromising blood pressure control and the ability of ACE inhibition to slow the progression of CKD.
- B. A low-salt, high-potassium diet can lower systolic blood pressure in hypertensive, otherwise normal individuals.
- C. High-salt diets interfere with diuretic therapy and should be avoided.
- D. Low-protein diets can reduce uremic symptoms in patients with advanced CKD.
- E. All of the above

Answer: E References 2 and 3 document that inadequate control of the diet counteracts the benefits of ACE inhibitor therapy. Reference 4 has details about the low-salt, high-potassium DASH diet. References 5 and 6 provide information that excess dietary salt overcomes the benefits of diuretics and how CKD-induced metabolic problems can be ameliorated by modifying the diet.

2. Zoccali C, Ruggenenti P, Perna A, et al. Phosphate may promote CKD progression and attenuate renoprotective effect of ACE inhibition. *J Am Soc Nephrol*. 2011;22:1923-1930.

3. Vegter S, Perna A, Postma MJ, et al. Sodium intake, ACE inhibition, and progression to ESRD. *J Am Soc Nephrol*. 2012;23:165-173.

4. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med*. 1997;336:1117-1124.

5. Kelly RA, Wilcox CS, Mitch WE, et al. Response of the kidney to furosemide. II. Effect of captopril on sodium balance. *Kidney Int* 1983;24: 233-239.

6. Mitch WE, Remuzzi G. Diets for patients with chronic kidney disease, still worth prescribing. *J Am Soc Nephrol*. 2004;15:234-237.

3. A 30-year-old man who has become an expert in computer-based games has been told he has kidney disease and needs dialysis. He comes to you for a second opinion. His physical examination reveals 3+ edema and a blood pressure of 200/98 mm Hg plus. Abnormal blood chemistry values include the following: serum creatinine, 2 mg/dL; blood urea nitrogen (BUN), 50 mg/dL; serum potassium, 5

mEq/L; serum bicarbonate, 16 mM/ μ L; and serum phosphorus, 6.2 mg/dL. Which of the following initial evaluations will be most helpful in the treatment of the patient?

- A. A discussion of the role of dialysis in avoiding complications of end-stage renal disease
- B. A careful family history to determine if there are inherited kidney diseases and potential family members who might donate a kidney
- C. A dietary history plus collection of a 24-hour urine specimen to measure the content of urea nitrogen, creatinine, albumin, and sodium
- D. Administration of hydralazine and amlodipine to reduce his blood pressure
- E. Measurements of calcitriol and 25-hydroxyvitamin D3 levels. If the values are low, supplement him with vitamin D. To compensate for protein losses, patients with the nephrotic syndrome should gain 2.5 to 3.5 g/kg of nonedematous body weight daily.

Answer: C The patient has complications of CKD, but the degree of CKD is within stage 3 (estimated glomerular filtration rate, 45 mL/min/1.73 m²). The 24-hour urine sample can guide dietary changes to reduce complications of CKD. His urinary albumin-to-creatinine ratio will provide more information about the severity of CKD, and his excretion of urea nitrogen will be used to restrict dietary protein to lower his BUN and to correct the retention of phosphates and acid. Sodium excretion will be used to design a salt-restricted diet because the patient has hypertension and edema. A and B: the degree of CKD is too low to consider dialysis or transplantation at this time. D: the preferred antihypertensive drug is an ACE inhibitor or angiotensin receptor blocker, and it will be difficult to correct his blood pressure without diuresis and dietary salt restriction. E: because he remains inside to play computer games, he may have low vitamin D levels. However, he has an elevated serum phosphorus level, which is a contraindication to vitamin D administration.

Ch / 132 **APPROACH TO THE PATIENT WITH GASTROINTESTINAL DISEASE**

1. A 60-year-old man reports the recent onset of mild to moderate epigastric pain during the last few weeks. The pain is unrelated to meals and does not radiate. He has had some decrease in appetite but no nausea, vomiting, weight loss, or dysphagia. He denies ingestion of any aspirin or nonsteroidal anti-inflammatory drugs. He tried taking an over-the-counter H₂-receptor antagonist (ranitidine) without symptomatic improvement. Physical examination findings are normal except for mild tenderness in the epigastrium. A stool specimen is negative for occult blood. Which of the following is the *most* appropriate initial diagnostic test?

- A. Upper gastrointestinal endoscopy
- B. *H. pylori* serology
- C. Abdominal computed tomography scan
- D. Ambulatory pH/impedance test
- E. An upper gastrointestinal series of radiographs, with a barium swallow

Answer: A The patient has dyspepsia (i.e., mild to moderate epigastric pain or discomfort), which is of recent onset but is not associated with any “alarm features.” Current guidelines recommend upper gastrointestinal endoscopy in patients with recent onset of dyspepsia who have alarm features or who are older than 55 years because of an increased likelihood of significant medical disorders, including peptic ulcer disease, gastroesophageal reflux disease, and malignant disease. Gastric biopsy specimens should be obtained to exclude *H. pylori* infection, which may cause dyspepsia and peptic ulcer disease. In patients without alarm features who are younger than 55 years, testing for *H. pylori* should be performed with a stool antigen assay or a urea breath test, and eradication therapy should be given if the test result is positive. Patients who do not have *H. pylori* infection or whose symptoms persist after *H. pylori* eradication may be treated empirically with a proton pump inhibitor for 4 to 8 weeks. Patients with persistent symptoms should undergo upper gastrointestinal endoscopy. (Talley NJ, Vakil NB, Moayyedi P. American Gastroenterological Association Technical Review on the evaluation of dyspepsia. *Gastroenterology*. 2005;129:1756-1780.)

2. A 65-year-old man reports progressive unintentional weight loss of 25 pounds (10% of body weight) during the past 12 months. He reports no dysphagia, nausea, vomiting, or jaundice. His appetite remains good. He reports loose stools and excessive, foul-smelling flatus. He has a history of diabetes mellitus, for which he takes metformin and insulin. He has a prior history of heavy ethanol use but has been abstinent for several years. A physical examination is unrevealing, including a nontender abdomen and no organomegaly or abnormal masses. Initial blood work including a complete blood count, electrolytes, and liver chemistries is normal. Which of the following is the *most likely* cause of the patient's weight loss?

- A. Metformin
- B. Chronic pancreatitis
- C. Colon cancer
- D. Diabetic gastroparesis
- E. Pancreatic cancer

Answer: B The patient's unintentional weight loss of more than 5% of his former body weight is significant and warrants evaluation (see Fig. 132-4). The presence of loose stools and increased flatus is suggestive of malabsorption. Given his history of heavy alcohol use, chronic pancreatitis resulting in malabsorption and diabetes mellitus is the most likely cause of weight loss. Metformin can cause a number of gastrointestinal symptoms, including dyspepsia and diarrhea, but it does not cause malabsorption. Although the patient could have an underlying malignant neoplasm, nonmetastatic colon cancer usually does not cause significant weight loss, and malabsorption is not a typical finding with pancreatic cancer. Although gastroparesis can cause weight loss, the patient has no early satiety or vomiting to suggest this diagnosis. (Forsmark CE. Management of chronic pancreatitis. *Gastroenterology*. 2013;144:1282-1291.)

3. A 73-year-old woman reports the onset of a constant aching, nonradiating left lower quadrant pain 2 days ago. She has continued to eat without nausea or vomiting, but her appetite is poor. She has not had a bowel movement for 2 days but has continued to pass flatus without relief of her discomfort. She has had no fever or chills. Her past medical history is noncontributory. She has chronic constipation but has noted no recent changes in her bowel habits. On physical examination, she is alert and moves without obvious pain. She has a normal blood pressure and pulse, with a temperature of 38° C. Bowel sounds are present but diminished. She has no tenderness to cough or percussion. On light and deep palpation, tenderness is noted in the left lower quadrant with some guarding. A mass is not palpable on abdominal or pelvic examination. Digital rectal examination is normal. Her white blood cell count is 12,000/ μ L. Which is the *most likely* cause of abdominal pain?

- A. Acute appendicitis
- B. Diverticulitis
- C. Colon cancer
- D. Ovarian torsion
- E. Pancreatic cancer

Answer: B The patient presents with 2 days of left lower quadrant pain without signs or peritoneal irritation (see Table 132-2 and Fig. 132-1). Although appendicitis must be considered, it uncommonly is manifested with pain in the left lower quadrant. An obstructing cancer in the distal colon can cause acute large bowel obstruction, but the absence of a change in her bowel habits and the presence of acute, localized pain make this diagnosis unlikely. Ovarian torsion can present at any age, usually with a more sudden onset of intense pain. The absence of a mass on pelvic examination makes this diagnosis unlikely. Pancreatic cancer pain usually has a more insidious onset with gradual progression. Diverticulitis usually is manifested with left lower quadrant pain because diverticulosis is more common in the left colon. The pain, which may be intermittent or constant, commonly is associated with obstipation or diarrhea. Diverticulitis may be associated with localized inflammation and microperforation, with formation of an inflammatory mass and abscess, or with free perforation and peritonitis. Abdominal CT with oral and intravenous administration of contrast material has a high sensitivity and specificity (>90%) for the diagnosis of diverticulitis and helps exclude other cause of

acute abdominal pain. (Biondo BS, Lopez Barao J, Millan M, et al. Current status of the treatment of acute colonic diverticulitis: a systematic review. *Colorectal Dis.* 2012;14:e1-e11.)

Ch / 134 **GASTROINTESTINAL ENDOSCOPY**

1. A 22-year-old woman with recurrent right upper quadrant pain is admitted for another attack. She undergoes an ultrasound and computed tomography (CT) examination of the abdomen, which does not reveal any significant abnormalities. Routine chemistries reveal mild ($<2\times$) elevations in transaminases. She is thought to have sphincter of Oddi dysfunction and is scheduled for sphincter manometry followed by possible endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy. What is the most important measure to prevent pancreatitis after this procedure?
- A. Octreotide given subcutaneously before the procedure
 - B. Rectal indomethacin right after the procedure
 - C. Intravenous antibiotics 6 hours before the procedure
 - D. Performance of the procedure under general anesthesia
 - E. Pancreatic enzymes begun before and continued after the procedure

Answer: B A single indomethacin suppository administered to patients immediately after ERCP significantly reduces the risk for pancreatitis compared with placebo in high-risk patients. Other measures have not been shown to be of value in this setting.

2. A 55-year-old man undergoes colonoscopy for colorectal cancer screening. The colonoscopy does not reveal any pathologic lesions. On recovery, as you discuss these results with the patient, he points out that his mother's cousin recently died of colorectal cancer. On hearing this, which of the following is most appropriate?
- A. Reassure the patient and schedule the next colonoscopy at 10 years.
 - B. Express concern about the family history and bring the patient back for another colonoscopy within a year.
 - C. Schedule the next colonoscopy at 3 years.
 - D. Schedule the next colonoscopy at 5 years.
 - E. Schedule CT colonography (or virtual colonoscopy) within the next 3 months in case you missed something.

Answer: A Only a history of colorectal cancer or adenoma in a first-degree relative is deemed to put a patient at higher risk than the general population. Therefore, a standard interval of 10 years after a normal screening colonoscopy is recommended.

3. A 35-year-old man presents with recent-onset dysphagia. He admits to occasional heartburn but no chest pain. He does not smoke or drink, and there is no family history of relevance. You perform an upper endoscopy, which reveals a smooth large bulge in the lateral wall of the midesophagus with normal-appearing overlying mucosa. Endoscopic biopsy findings are normal. Your next step is to
- A. Reassure the patient and bring him back for another endoscopy within 6 months or a year to monitor the progress of the lesion
 - B. Refer the patient for surgery
 - C. Schedule the patient for a CT scan of the chest
 - D. Schedule the patient for an endoscopic ultrasound
 - E. Dismiss the finding as a normal variant and treat the patient with a course of antireflux medications.

Answer: D These findings suggest a submucosal lesion such as a leiomyoma. The best way to determine its origin is by endoscopic ultrasound, which can also detect any enlarged nodes that may be targeted for cytologic aspiration.

4. A 67-year-old man is being worked up for iron deficiency anemia. Occult blood is detected in the stool, and he undergoes an upper endoscopy and colonoscopy, both of which have normal findings, except for diverticulosis of the colon. Which of the following would you recommend?

- A. Trial of iron infusion therapy and monitor blood counts during the next year
- B. Empirical trial of estrogen therapy for suspected (occult) telangiectasia of the intestine
- C. Proceed to enteroscopy
- D. Schedule a capsule endoscopy
- E. Refer to a surgeon for exploration of the small bowel by laparoscopy for occult tumor

Answer: D Capsule endoscopy is the procedure of choice to examine the mucosa of the small bowel because of its accuracy and noninvasive nature. If a lesion requires further intervention (biopsy, removal), deep enteroscopy may be undertaken, depending on its nature and location within the small bowel.

5. An 82-year-old man admitted to the orthopedic service after back surgery complains of progressively distended abdomen and obstipation. A plain radiograph of his abdomen reveals marked dilation of the colon, with a cecal diameter of 9 cm. Despite correction of hypokalemia and a trial of neostigmine, there is no improvement. On examination, his abdomen is visibly distended but not tender, and there are no peritoneal signs. The next step for this patient is

- A. Trial of intravenous erythromycin
- B. Continue with nasogastric suction and intravenous rehydration for another 48 hours
- C. Colonoscopy with attempted decompression
- D. Immediate surgery and exploration for mechanical obstruction
- E. Urgent cecostomy

Answer: C This patient has acute colonic pseudo-obstruction or Ogilvie syndrome. Neostigmine is a first medical measure if there are no cardiac contraindications. Because of the large size of his cecum, he is at risk for perforation if decompression is not successful. Decompression is best attempted with colonoscopy; if this procedure fails, a cecostomy is an appropriate further step.

1. A 50-year-old man without any prior medical problems began taking ibuprofen 800 mg three times daily for lower back pain after a work-related injury. He subsequently developed nausea followed by hematemesis and melena. He now presents to the emergency department for further evaluation. On the basis of this presentation and epidemiologic studies, what is the most likely cause of the suspected upper gastrointestinal (GI) hemorrhage?

- A. Peptic ulcer
- B. Mallory-Weiss tear
- C. Esophagitis
- D. Esophageal varices
- E. Dieulafoy lesion

Answer: A This patient began taking a nonsteroidal anti-inflammatory drug (NSAID) and subsequently presented with melena and hematemesis indicative of upper GI bleeding. Both epidemiologic data and the clinical history support peptic ulcer disease as the most likely cause of the bleeding. A Mallory-Weiss tear is possible on the basis of the clinical presentation but is less likely to be associated with NSAID use and is not the likely cause of his bleeding. (Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol*. 2012;107:345-360.)

2. A 70-year-old man who had a mechanical aortic valve implanted for aortic stenosis presents to the emergency department with painless hematochezia. He is receiving warfarin and takes aspirin 81 mg daily. He is volume resuscitated with 6 units of packed red blood cells and stabilized. An urgent colonoscopy demonstrates no fresh blood in the terminal ileum or colon. There are a few, scattered diverticula. What would you do next?

- A. Upper endoscopy
- B. Tagged red blood cell scan
- C. Nothing
- D. Angiography
- E. Surgery

Answer: A This patient presents with hematochezia that is suggestive of a lower bleeding source. However, up to 15 to 18% of cases of significant hematochezia have an upper GI tract cause, such as peptic ulcer or esophageal varices. For this reason, the patient should be further evaluated with an upper GI endoscopy. As a matter of routine practice, high-volume hematochezia (as indicated by hemodynamic compromise, high volume requirements for volume resuscitation, and a large fall in the hematocrit, particularly when it occurs in conjunction with risk factors for peptic ulceration or portal hypertension) should prompt an urgent upper GI endoscopy as the first intervention after resuscitation, followed by a rapid bowel purge and colonoscopy. (Kovacs TOG, Jensen DM. Upper or small bowel hemorrhage that presents as hematochezia. *Tech Gastrointest Endosc*. 2001;3:206-215; Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol*. 2012;107:345-360.)

3. A 80-year-old woman presents with melena, hematemesis, and syncope. Examination reveals hypotension and tachycardia. What is the first step in management?

- A. Emergent endoscopy
- B. Nasogastric lavage
- C. Intravenous proton pump inhibitor
- D. Tagged red blood cell scan
- E. Intravenous access and intravascular volume repletion

Answer: E The first step in any active GI hemorrhage is volume resuscitation. In this scenario, the patient has lost at least 50% of her intravascular volume, so aggressive resuscitation with both blood and crystalloid products is required. Emergent endoscopy (A), intravenous proton pump inhibitor (C), and nasogastric lavage (B) may be necessary, but only after adequate repletion of the intravascular

volume. In general, few patients die of complete exsanguination, particularly in the setting of peptic ulcer bleeding, whereas the majority die as a consequence of the physiologic impact of sudden, dramatic volume shifts, with a disproportionate mortality in the elderly, who may suffer a stroke, myocardial infarction, and acute renal failure if they are not volume resuscitated promptly. Volume resuscitation is initiated with saline, and it is inappropriate to delay while waiting for blood transfusion. (Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol*. 2012;107:345-360.)

4. A 70-year-old man with a history of coronary artery disease is admitted to the hospital for melena and dizziness. He takes aspirin 81 mg daily for secondary prophylaxis of cardiovascular disease without concurrent acid suppression. Endoscopy reveals an antral ulcer with a nonbleeding visible vessel that is treated with endoscopic hemostasis. Biopsy shows no evidence of *H. pylori*. He is started on a proton pump inhibitor (PPI). What would be the best course of action?
- A. Continue PPI daily and do not restart aspirin.
 - B. Continue PPI daily and restart aspirin in 4 to 6 weeks.
 - C. Continue PPI daily and restart aspirin within 1 week.
 - D. Stop PPI in 4 to 6 weeks and restart aspirin on discharge.
 - E. Stop PPI and restart aspirin in 4 to 6 weeks.

Answer: C In patients who need aspirin for cardioprotection, the antiplatelet agent should be restarted as soon as cardiovascular risks outweigh GI risks. In a study of patients randomized to restart aspirin versus placebo soon after endoscopic treatment of bleeding ulcer disease, those taking aspirin had more bleeding but significantly lower mortality and cardiovascular events. Therefore, aspirin usually should be restarted within the first week after endoscopic therapy while continuing PPI therapy as well. (Sung JJ, Lau JY, Ching JY, et al. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Ann Intern Med*. 2010;152:1-9.)

5. A 70-year-old woman presents to the emergency department with dizziness and five episodes of bright red blood per rectum in the last 24 hours. Nasogastric tube lavage yields bilious fluid without blood. What is the most common cause of severe hematochezia?
- A. Diverticulosis
 - B. Colonic angiodysplasia
 - C. Internal hemorrhoids
 - D. Ulcerative colitis
 - E. Ischemic colitis

Answer: A Diverticulosis, which is the most common cause of severe hematochezia, accounts for about one third of the colonic sources of severe hematochezia. Internal hemorrhoids and ischemic colitis are the next most common causes. Diverticular hemorrhage may be self-limited, but in severe cases, either colonoscopy or angiography can find and treat the bleeding diverticulum. Several studies have shown at least some benefit of early colonoscopy compared with radiologic testing to determine the location of bleeding and to decrease overall cost. (Jensen DM. The ins and outs of diverticular bleeding. *Gastrointest Endosc*. 2012;75:388-391.)

1. Which of the following is a likely cause of duodenal ulceration in patients who are *Helicobacter pylori* negative?

- A. Bordetella pertussis infection
- B. Zollinger-Ellison syndrome
- C. Pheochromocytoma
- D. Mercury poisoning
- E. None of the above

Answer: B Zollinger-Ellison syndrome is caused by a gastrin-producing endocrine tumor, which is usually in the pancreas or small bowel and leads to marked hyperacidity. This syndrome usually gives rise to severe peptic ulcer disease with multiple, concomitant duodenal ulcers that are resistant to conventional acid suppressive therapy. The other conditions listed are not known to be associated with an increased risk for peptic ulcer.

2. An 80-year-old woman with degenerative joint disease involving her fingers presents with a gastric ulcer with smooth edges. She denies being prescribed nonsteroidal anti-inflammatory drugs (NSAIDs), and biopsies and serology for *H. pylori* are negative. Which of the following is the most likely cause of her ulcer?

- A. Gastric rheumatoid nodules
- B. Systemic lupus erythematosus
- C. Over-the-counter medications containing NSAIDs
- D. Ankylosing spondylitis
- E. Surreptitious laxative abuse

Answer: C Over-the-counter NSAID use is very common, in particularly in elderly patients. Patients often do not recognize that they use NSAIDs even when specifically asked. Targeted questioning and checking of home medication is therefore indicated. In some series, surreptitious use of NSAIDs or aspirin was found as the underlying cause in 30 to 60% of patients with previously unexplained peptic ulcer.

3. Which of the following is the major factor contributing to current changes in the incidence of peptic ulcer disease in developed countries?

- A. The rise in *H. pylori*-associated gastric ulcers
- B. The fall in NSAID-associated duodenal ulcers
- C. The rise in NSAID-related gastric ulcers
- D. The rise in NSAID-related duodenal ulcers
- E. The rise in intensive care unit (ICU)-related stress ulcers

Answer: C *H. pylori*-related ulcers have considerably decreased in developed countries owing to a decrease in the declining prevalence of the bacterium in recent generations and the use of eradication therapy. ICU-related stress ulcers have become less common owing to improvements in overall management, including respiratory and hemodynamic care, acid inhibition, and emphasis on adequate feeding. NSAID use has become more common and has given rise to an increase of NSAID-related ulcer disease.

4. Which of the following is correct about peptic ulcer disease?

- A. Risk is greatest in females.
- B. The highest relative risk is in persons younger than 20 years.
- C. Treatment of autoimmune diseases with biologic agents (e.g., anti-tumor necrosis factor [TNF]- α agents) has increased risk.
- D. Most deaths are due to gastric cancer.
- E. Smoking increases risk.

Answer: E Peptic ulcer is more common in men and in elderly people. Anti- TNF- α treatment is not causally related to peptic ulcer disease, and most patients with peptic ulcers do not develop gastric cancer. In *H. pylori*-positive subjects, however, smoking increases the risk for peptic ulceration. This increased relative risk has been reported to be up to 12-fold.

5. Which of the following involves an increased risk for peptic ulcer disease?

- A. Scleroderma
- B. Pernicious anemia
- C. Celiac disease
- D. Systemic mastocytosis
- E. Cryptococcosis

Answer: D In vitamin B12 deficiency with pernicious anemia, gastric atrophy is caused by an autoimmune gastritis. However, this inflammation is not associated with peptic ulcer disease. Autoimmune inflammation of the small bowel due to celiac disease also does not cause ulceration. Various infectious conditions can give rise to peptic ulcer, but cryptococcosis is not one of them. Systemic vasculitides can be associated with peptic ulcers, but they are not a common presenting manifestation of scleroderma. Systemic mastocytosis is, however, associated with a clearly increased risk for peptic ulceration.

6. The effect of *H. pylori* eradication therapy always needs to be assessed in patients with which of the following?

- A. A bleeding peptic ulcer
- B. Reflux esophagitis
- C. Nonulcer dyspepsia
- D. Uncomplicated peptic ulcer
- E. Chronic active gastritis

Answer: A Patients with complicated peptic ulcer disease, such as peptic ulcer bleeding, are at considerably increased risk for recurrent ulcer complications. Patients with previous peptic ulcer bleeding in the presence of *H. pylori* therefore always need to be assessed to document the success of eradication therapy. If treatment has failed, they need repeat eradication treatment.

7. Which of the following statements is *false* in patients with peptic ulcer bleeding?

- A. Endoscopic treatment is the mainstay of therapy.
- B. Preemptive proton pump inhibitor (PPI) therapy reduces the need for endoscopic treatment.
- C. High-dose continuous intravenous PPI treatment reduces the risk for rebleeding.
- D. Patients with a low Blatchford score usually do not require intervention.
- E. Recurrent bleeding requires surgery.

Answer: E In patients with peptic ulcer bleeding, endoscopic treatment is the mainstay to stop ongoing bleeding and reduce the risk for rebleeding. Preemptive PPI therapy reduces the need for endoscopic treatment, but it has no effect on rebleeding and mortality. High-dose continuous intravenous PPI treatment reduces the risk for rebleeding, the need for blood transfusion, and mortality in patients with a high risk for rebleeding. The Blatchford scale can be used to predict the need for intervention, such as endoscopic treatment and blood transfusion; a low score is associated with a low chance that an intervention is needed. Patients with recurrent bleeding despite endoscopic and PPI treatment can often first be retreated endoscopically. If this retreatment fails, both angiographic embolization of the feeding vessel and surgery are alternative rescue treatments. Recurrent bleeding is thus not a routine indication for surgery.

1. Which one of the following complications is a known consequence of long-standing ulcerative colitis?

- A. Fecaluria (as a manifestation of fistula formation to the bladder from adjacent loops of bowel)
- B. Perianal abscess formation
- C. Colonic stricture formation with subsequent small bowel obstruction
- D. Development of dysplasia and carcinoma
- E. Development of left-sided hydroureter

Answer: D The transmural inflammatory process of Crohn disease (but not ulcerative colitis) predisposes to the formation of fistulas, and the presence of fistulae signifies that the transmural inflammation has penetrated into adjacent organs, tissue, or skin. Ulcerative colitis is limited to the colon and, unlike Crohn disease, does not cause perianal abscesses. In Crohn disease, inflammation can lead to ileal or colonic strictures, and marked inflammation can cause local reactions that have a mass effect and lead to obstruction of the right ureter, where the ileum and the ureter cross anatomically. Patients with ulcerative colitis do not develop strictures or hydroureter. Dysplasia and carcinoma may develop in patients with longstanding Crohn disease but are much more typical of ulcerative colitis. This risk provides the rationale for endoscopic surveillance of patients with long-standing inflammatory bowel disease.

2. Which one of the following features is most typical for ulcerative colitis?

- A. Deep serpiginous ulcers
- B. Aphthous ulcers
- C. Pseudopolyps
- D. Fistulas
- E. Colonic stricturing

Answer: C Pseudopolyps are typically found in patients with ulcerative colitis, not in patients with Crohn disease. Typical radiologic and endoscopic features of Crohn disease include deep linear ulcers and superficial or aphthous ulcers overlying lymphoid follicles. The presence of fistulas should signal the presence of Crohn disease. Patients with Crohn disease may have strictures, which are not classically seen in ulcerative colitis. When strictures are observed in patients with ulcerative colitis, coexisting colorectal cancer should be suspected.

3. Which one of the following statements regarding mesalamine (5-ASA) is true?

- A. Oral mesalamine is effective for the induction and for the maintenance of remission in patients who have Crohn disease with a colonic disease distribution.
- B. Topical mesalamine for ulcerative proctitis (suppositories) and for left-sided ulcerative colitis (enemas) is effective for the induction and maintenance of remission.
- C. Mesalamine is first-line therapy for patients with moderate to severe ulcerative colitis.
- D. Mesalamine is efficacious as primary therapy for perianal fistulizing Crohn disease when active disease is present in the rectum.
- E. A combination of topical and oral mesalamine therapy in patients with left-sided Crohn disease is more effective than topical or oral mesalamine alone.

Answer: B Oral mesalamine is effective for inducing and maintaining remission in mild to moderate ulcerative colitis. Mesalamine suppositories treat the lower 10 to 20 cm of the colon but do not reach the left colon or splenic flexure; they are extremely effective for inducing and maintaining remission in ulcerative proctitis. In contrast, mesalamine liquid enemas will reach the left colon and as high as the splenic flexure; they are extremely effective for inducing and maintaining remission in left-sided ulcerative colitis. Both oral and topical therapies are effective for treating patients with active ulcerative colitis, and the combination of topical and oral mesalamine therapy is more effective than either mesalamine therapy alone in patients with left-sided ulcerative colitis. Mesalamine is no more effective than placebo for inducing or maintaining remission in Crohn disease patients.

Ch / 142 **INFLAMMATORY AND ANATOMIC DISEASES OF THE INTESTINE, PERITONEUM, MESENTERY, AND OMENTUM**

1. An 18-year-old college freshman reports to the Student Health Center. He complains of a 12-hour history of abdominal pain and fever. He complains of anorexia, nausea, and vomiting. He denies diarrhea and blood per rectum. His past history is unremarkable. His family history is notable for heart disease, hypertension, and diverticulosis coli. On physical examination, he is febrile to 38° C. His abdomen has normal bowel sounds but is tender in the right lower quadrant with rebound tenderness. On laboratory examination, his WBC count is elevated at 11,000/μL with a left shift. His urinalysis reveals 1+ protein. The most likely diagnosis in this patient is

- A. acute colonic diverticulitis.
- B. ulcerative colitis.
- C. acute appendicitis.
- D. Behçet disease.
- E. nephrolithiasis and renal colic.

Answer: C This patient has an acute appendicitis. He has typical presenting signs and symptoms. Acute diverticulitis typically presents at an older age, and it most commonly localizes to the left side of the abdomen. Although ulcerative colitis presents at this age, its symptoms are typically bloody diarrhea and tenesmus. This patient does not have the multisystem presentation that is common for Behçet disease, in which small bowel involvement is rare. His normal urinalysis result makes a diagnosis of nephrolithiasis and renal colic unlikely.

2. A 64-year-old woman reports to the emergency department with a complaint of 2 days of left lower quadrant pain, fever, and diarrhea, as well as nausea and vomiting. She denies recent travel and antibiotic use. She admits to many years of constipation and uses laxatives intermittently. Her past history is notable for hypertension and glaucoma. Her medications include hydrochlorothiazide 25 mg/day and eye drops for glaucoma. Her family history is positive for hypertension, diabetes mellitus, and coronary artery disease. Her physical examination is notable for temperature of 37.6° C, and a heart rate of 105 beats/min. Heart examination shows a regular tachycardia and a grade 2/6 midsystolic murmur. Her abdomen is soft with tenderness in the left lower quadrant. There is no distention or involuntary rebound. On digital rectal examination, there is no stool in the rectal vault, and you palpate internal hemorrhoids. The most like diagnosis is

- A. Meckel diverticulum.
- B. acute colonic diverticulitis.
- C. Crohn colitis.
- D. colonic intussusception.
- E. acute intestinal obstruction.

Answer: B This patient has the typical presenting signs and symptoms of sigmoid colon diverticulitis. Complications from Meckel diverticulum, such as right lower quadrant pain from ulceration and bleeding, are not present. Crohn colitis can occur in this age group, but the presentation usually is more insidious with diarrhea and abdominal pain. The patient does not have the symptoms of bowel obstruction or the currant jelly stools that are typical of colonic intussusception.

3. An 82-year-old man is referred to the emergency department from a nursing home. He complains of abdominal distension and progressive constipation. He has not passed flatus or stool for 2 days. His history is notable for dementia and a prior stroke. He has used laxatives for constipation for many years. His other medications include clopidogrel and aspirin. He is allergic to intravenous contrast dye. On examination, you find he is afebrile with a blood pressure of 155/93 mm Hg and a tachycardia of 110 beats/min. His abdomen is distended and tympanic to percussion, with a diffuse tenderness. Bowel sounds are decreased. A small amount of stool in the rectal vault is brown but Hemoccult positive. Laboratory tests reveal a lactate of 2 and a normal WBC and Hgb levels. The next step in his management is

- A. exploratory laparotomy.
- B. abdominal radiographs.
- C. bleeding scan.
- D. mesenteric angiography.
- E. barium upper GI series.

Answer: B This patient has a sigmoid volvulus. A volvulus is commonly seen in institutionalized patients and in patients with a history of chronic constipation and laxative use. The presence of a volvulus or intestinal obstruction from other causes can be investigated cost effectively using plain radiographs as the initial imaging modality. There is no massive gastrointestinal (GI) bleeding to warrant a bleeding scan, angiography, or upper GI series.

4. A 55-year-old woman presents to your office complaining of vague abdominal pain and fatigue. Her past history is notable for osteoarthritis. She is postmenopausal and on hormone replacement therapy. Her medications also include ibuprofen 600 mg tid. She has noted intermittent black tarry stools. Physical examination is unremarkable. Laboratory examination reveals Hgb 8.7 g/dL with an MCV 79. You obtain an esophagogastroduodenoscopy (EGD) and a colonoscopy for her anemia and abdominal complaints. EGD is normal, and she has mild sigmoid diverticulosis coli. The most likely cause of her anemia is
- A. diverticular bleeding.
 - B. gastric ulcer bleeding.
 - C. Meckel diverticulum.
 - D. Crohn disease.
 - E. NSAID-induced enteropathy.

Answer: E This patient has nonsteroidal anti-inflammatory drug (NSAID)-induced enteropathy. The episodes of melena are suggestive of ulceration and bleeding from the upper gastrointestinal (GI) tract, but peptic ulcer disease was not seen on EGD. She regularly uses NSAIDs, which can be a cause of secondary small intestinal ulcerations. Meckel diverticulum and bleeding are more rare than NSAID-induced enteropathy. Although sigmoid diverticuli were identified on colonoscopy, diverticular bleeding presents as massive lower GI bleeding, not melena. Crohn disease can present with anemia and bleeding, but melena is rare.

5. A 63-year-old man presents to your office with a complaint of 5 months of a poor appetite, a 35-lb weight loss, and low grade fevers up to 37.4° C. Over the past month, he has noted increasing abdominal girth and tenderness. He has been otherwise healthy and takes no medications. His family history is notable for stroke. He denies tobacco use. He drinks two glasses of wine each night. He retired at age 55 years and has traveled extensively throughout Southeast Asia. On physical examination, you note that his abdomen is markedly distended and diffusely tender. Bowel sounds are normal, but a fluid wave is present. Findings of the laboratory examination, including a comprehensive metabolic profile and complete blood count, are normal. A diagnostic paracentesis reveals protein, 3.5 g/dL; neutrophils, 800/μL; glucose, 20 mg/dL; and amylase, 50 IU/L. No bacteria are seen on stain, and fluid cultures show no growth. The most likely diagnosis for this man's ascites is
- A. alcoholic cirrhosis.
 - B. pancreatic ascites.
 - C. nephrotic syndrome.
 - D. metastatic lung cancer.
 - E. tuberculous peritonitis.

Answer: E This patient has tuberculous peritonitis, which characteristically presents insidiously in patients who have been exposed to tuberculosis, as this patient probably was exposed during extensive travel in endemic regions like Southeast Asia. The ascites is typically high in protein and neutrophils and low in glucose. The patient's alcohol use and the characteristics of his ascites make alcoholic cirrhosis an unlikely cause. The ascitic fluid amylase level is normal, so pancreatic ascites is

unlikely. Ascitic fluid in adult patients with the nephrotic syndrome is low in protein and is associated with hypoalbuminemia and heart failure. The characteristics of his ascites are not typical of metastatic carcinomatosis.

Ch / 144 **PANCREATITIS**

1. A 52-year-old man is admitted with presumed acute alcoholic pancreatitis. On admission, his blood pressure is 111/60 mm Hg, pulse is 110 beats/min, respiration rate is 18 breaths/min, and temperature is 37.8° C. His initial physical examination is notable for a tender abdomen without rebound but is otherwise normal. Initial laboratory results include a WBC of 14,000/ μ L, Hgb 14.1, normal electrolytes, BUN of 26, creatinine of 1.2, and lipase of 720. Liver tests, calcium, and the triglyceride level are normal. Ultrasonography in the emergency department notes a normal gallbladder and bile duct. A computed tomography scan obtained in the emergency department notes some peripancreatic fluid and haziness of the peripancreatic fat. He is admitted to an intermediate care unit and treated with vigorous fluid resuscitation, antiemetics, and analgesics. On day 2, his blood pressure and pulse have normalized, but he has developed a low-grade fever of 38.1° C. He continues to have significant pain and some nausea. A CT scan obtained on day 3 now reveals that 40% of the pancreas is necrotic; there is no gas in the necrotic area. Fever continues with a maximum temperature of 38.2° C, the WBC is still 14,000/ μ L with a left shift. What would you recommend now?

- A. Initiate imipenem.
- B. Perform a fine-needle aspiration (FNA) and culture of the necrotic collection.
- C. Place a percutaneous drain in necrotic collection.
- D. Obtain a surgical consultation.
- E. Continue the current conservative therapy.

Answer: E The patient has moderately severe acute pancreatitis with necrosis. Prophylactic antibiotics are not recommended. Infection of the necrosis usually occurs after 1 to 2 weeks of disease, and the clinical features and imaging are not suggestive of infection; as a result, FNA is not needed. The necrosis is not yet walled off or liquefied, so placement of a drain in the collection would be harmful. There is no indication for surgery in this patient. Conservative therapy, which could include placement of a nasoduodenal tube to initiate nutrition, should be continued.

2. A 42-year-old woman is seen in the emergency department with abdominal pain, nausea, and vomiting over the past 12 hours. On physical examination, she is in obvious pain. She is tachycardic, but her vital signs are otherwise normal. Her general physical examination results are normal; her abdomen is mildly distended and tender to palpation without rebound. Laboratory results include amylase of 4500, AST of 220, ALT of 170, alkaline phosphatase of 200, total bilirubin of 1.8, WBC of 12,000/ μ L, and Hgb of 12; the remaining blood test results are normal. Abdominal ultrasonography reveals several small stones in the gallbladder; the common bile duct is 7 mm. A CT scan reveals interstitial pancreatitis. She is admitted and treated with intravenous fluid, antiemetics, and analgesics. On the following day, her AST is 140, ALT is 160, total bilirubin is 1.6, and WBC is 11,000/ μ L. She remains afebrile. What would you recommend now?

- A. Initiate antibiotics
- B. Urgent endoscopic retrograde cholangiopancreatography
- C. Repeat ultrasonography now
- D. Endoscopic ultrasonography now
- E. Continue current conservative therapy

Answer: E This patient has gallstone pancreatitis, which is resolving. There are no features to suggest concomitant cholangitis, and liver chemistries are improving. Urgent ERCP is not required. Prophylactic antibiotics are likewise not indicated. There is no reason to repeat the ultrasonography, and the liver chemistries are improving. An EUS is not needed because there is no clinical concern for microlithiasis. Continued conservative management is appropriate.

3. You see a 58-year-old man who was recently discharged after a 2-week admission for acute pancreatitis. The cause of the pancreatitis is not known, his liver chemistries and triglycerides were normal, and his abdominal ultrasonography revealed no gallstones. He does not drink but does smoke; he was on no medications known to cause pancreatitis. He is now feeling well. A CT scan during the hospitalization revealed enlargement of the head of the pancreas with peripancreatic fluid and stranding but no necrosis. What would you recommend now?

- A. Serum IgG4 level
- B. Endoscopic ultrasonography
- C. Genetic testing
- D. ERCP
- E. No further testing unless a second attack occurs

Answer: B This patient with an unexplained episode of pancreatitis and at an age older than 40 years must be evaluated for the possibility of malignancy underlying his unexplained pancreatitis. Endoscopic ultrasonography (EUS) provides the most effective method to search for underlying malignancy and to exclude microlithiasis. Genetic testing might be considered if his EUS results are negative. The patient might have autoimmune pancreatitis, but this is a diagnosis of exclusion.

4. A 28-year-old woman is evaluated as an outpatient for chronic abdominal pain. This is her first visit with you, and she reports that she has chronic pancreatitis. The pain is continuous, epigastric, without radiation, and has been present for 2 years. She has not lost weight, does not smoke or drink, and has no family history of pancreatic disease. She is currently treated with oxycodone four times daily, with little relief of pain. You obtain previous medical records, which include several emergency department visits; on one of these visits, her amylase was elevated to 156 (normal <140). Results of several CT scans obtained during these visits were normal. Her physical examination result is normal. Results of laboratory tests, including amylase, lipase, liver chemistries, and triglycerides, are normal. What would you recommend now?

- A. ERCP
- B. EUS
- C. Celiac plexus block
- D. Initiate gabapentin
- E. Fecal elastase

Answer: B This patient has a chronic pain syndrome but does not have sufficient evidence of chronic pancreatitis. ERCP is not indicated as a diagnostic procedure. Celiac plexus block would only be considered if a diagnosis of chronic pancreatitis was confirmed and even then only in rare circumstances. Gabapentin as an adjunctive agent is reasonable but again only after an accurate diagnosis is made. Fecal elastase would be normal in this patient; even if she has chronic pancreatitis, it is not far enough advanced for fecal elastase to be abnormal. EUS provides the best method to assess this patient for chronic pancreatitis.

5. A 52-year-old man with an 8-year history of chronic pancreatitis attributable to alcohol and tobacco is evaluated for weight loss. He has chronic pain that is managed with tramadol. He has also been treated with pancreatic enzymes and is currently taking 20,000 units of an enteric-coated lipase preparation with each meal. He notes a 20-lb weight loss over the past 6 months. He reports a normal appetite but does have some loose stools. His physical examination is notable for evidence of weight loss. Laboratory testing includes a normal CBC, amylase, and lipase. A CT scan reveals a dilated pancreatic duct with diffuse pancreatic calcifications. Fecal elastase is 85 mcg/g of stool. What would you recommend now?

- A. Empiric treatment for small intestinal bacterial overgrowth
- B. Add a proton pump inhibitor
- C. Increase pancreatic enzyme dosage
- D. Pancreatic duct stent
- E. Refer for pancreatic surgery

Answer: C This patient has exocrine insufficiency and is on an inadequate dose of enzymes (which should be at least 50,000 units of lipase with each meal and up to 90,000 units). Small intestinal bacteria overgrowth might be considered if he fails to respond to an appropriate dose of enzymes. Acid suppression is not needed with enteric-coated preparations. Placement of a pancreatic duct stent or surgery might be considered for intractable pain, but this patient has pain manageable with simple medical measures.

Ch / 145 **DISEASES OF THE RECTUM AND ANUS**

1. A 34-year-old man presents with perianal pain, fever, and leukocytosis. Physical examination demonstrates no obvious source. Which of the following is the most appropriate next step?

- A. Repeat examination in 24 hours
- B. 10-day course of oral antibiotics
- C. Digital rectal examination
- D. Office-based needle aspiration
- E. Examination under anesthesia

Answer: E Supralevator, intersphincteric, and deeper abscesses may present with symptoms but no obvious source on physical examination. Although adjunctive radiological testing can be considered, the best approach to this potentially serious and urgent problem is examination under anesthesia. Antibiotics alone will not resolve an abscess that needs to be drained. Digital rectal examination and blind needle aspiration in the office should be avoided.

2. A 55-year-old otherwise healthy woman complains of a mass at her anal verge with straining. Which of the following is the most characteristic for differentiating rectal prolapse from other anorectal disorders?

- A. Presence of radial folds
- B. Concomitant bleeding
- C. Presence of concentric mucosal folds
- D. A patulous anal sphincter
- E. Associated incontinence

Answer: C The diagnosis of rectal prolapse is made clinically, with the major finding of concentric mucosal folds—the so-called “bulls eye.” The presence of radial folds is seen in mucosal and hemorrhoidal prolapse. Although bleeding, incontinence, and a patulous anus may be seen in rectal prolapse, each may be also present in many other anorectal disorders and none are specific for rectal prolapse.

1. Fever is a frequent feature of which of the following?

- A. Acute alcoholic hepatitis
- B. Acute hepatitis C
- C. Autoimmune hepatitis
- D. Chronic hepatitis B
- E. Chronic hepatitis C

Answer: A With the exception of the prodrome of acute hepatitis A, fever is not prominent in viral hepatitis nor in autoimmune hepatitis. It is a feature of acute alcoholic hepatitis even in the absence of infection.

2. Which of following suggests biliary obstruction as the cause of scleral icterus?

- A. Dark urine and dark stool
- B. Pale urine and pale stool
- C. Dark urine and pale stool
- D. Dark urine and alternating pale and dark stool
- E. Pale urine and dark stool

Answer: C With jaundice from biliary obstruction, bilirubin is predominantly conjugated, water-soluble, and excreted in the urine, which is therefore dark. Because of biliary obstruction, bile salts cannot reach the intestine, so stools are pale. By comparison, the excess bilirubin from hemolysis is unconjugated and not water soluble, so it is not excreted in the urine.

3. Which of the following presentations suggests variceal hemorrhage?

- A. Unexplained iron deficiency anemia
- B. Dysphagia
- C. Abdominal bloating
- D. Abdominal pain
- E. Hematemesis

Correct: E Variceal hemorrhage is typically profuse, painless, and not associated with esophageal symptoms such as dysphagia. Because bleeding is overt, unexplained iron deficiency is not usually due to bleeding varices.

4. Which of the following disorders has an autosomal dominant inheritance?

- A. Wilson disease
- B. Hemochromatosis
- C. α 1-Antitrypsin deficiency
- D. Adult polycystic disease
- E. Hepatic adenoma

Correct: D Adult polycystic disease has an autosomal dominant inheritance, whereas the other conditions are sporadic, such as adenoma, or autosomal recessive, such as Wilson disease.

1. A 51-year-old man presents with 3 months of painless jaundice, pale stools, and dark urine, as well as spiking fevers. His Hgb is 10.2 g/dL; WBC 6500/ μ L with 64% PMNs; and platelets 145,000. Total bilirubin is 28 mg/dL; direct-reacting bilirubin 21 mg/dL; alkaline phosphatase 336, AST 94, ALT 116, albumin 3.1, PT INR 1.8. Urine urobilinogen is undetectable, and urine bilirubin is +++. Abdominal ultrasound shows proximal dilatation of the intrahepatic bile ducts, and magnetic resonance cholangiopancreatography reveals a constricting mass in the common bile duct several centimeters distal to the junction of the right and left hepatic ducts. After being started on intravenous broad-spectrum antibiotics, the patient is taken to surgery, where the mass is resected and the common bile duct is anastomosed over a stent. Two weeks later his total bilirubin is 14 mg/dL, direct-reacting bilirubin 10 mg/dL, alkaline phosphatase 225, and urine urobilinogen still undetectable. Urine bilirubin is also undetectable. Because of the persistent direct-reacting hyperbilirubinemia and elevated alkaline phosphatase, the surgeon is considering taking the patient back to the operating room and re-exploring his biliary tract. Which of the following test results argues *against* that decision?

- A. Total bilirubin
- B. Direct-reacting bilirubin
- C. Alkaline phosphatase
- D. Urine urobilinogen
- E. Urine bilirubin

Answer: E After successful relief of chronic bile duct obstruction, both the total bilirubin and the alkaline phosphatase may take several weeks to normalize. The combination of elevated direct-reacting bilirubin in plasma and an absence of bilirubin from the urine indicates that the direct-reacting fraction in plasma now consists of δ -bilirubin, a covalent complex of conjugated bilirubin with albumin, that is not cleared by the kidney. Although the absence of urobilinogen from the urine at the time of admission reflected complete bile duct obstruction, its persistence after 2 weeks of broad-spectrum antibiotic therapy no longer reflects biliary obstruction, but rather elimination by the antibiotics of the bacteria necessary to convert bilirubin in the gut to urobilinogen. In this case, use of a dipstick that detects bilirubinuria could save the patient from an unnecessary second surgical procedure.

2. A 24-year-old nurse presented to the employee health department of her hospital complaining of arthralgias, weakness, and fatigue for 2 weeks. She had previously been in good health and had a normal physical examination, CBC, and metabolic panel, including serum bilirubin determination, at her annual physical examination 2 months earlier. Her family history included relatives with rheumatoid arthritis and lupus erythematosus. On physical examination she was pale, with faintly icteric sclerae and a palpable spleen tip. Her Hgb was 7.6, Hct 23%, reticulocytes 14%, plasma total bilirubin 2.1 mg/dL, direct-reacting bilirubin 0.2 mg/dL, and indirect bilirubin 1.9 mg/dL. A lupus erythematosus preparation was negative, but because a direct Coombs test was strongly positive, the diagnosis of autoimmune hemolytic anemia was made. She consented to participate in a research study and was found to have a normal hepatic bilirubin clearance (CBR) of 0.53 mL/min/kg (normal range: 0.65 ± 0.18 [SE]), a plasma bilirubin turnover of 14.4 mg/kg/day (normal: 3.9 ± 0.7), a circulating red blood cell mass of 15.3 mL/kg (normal: 25-35), and a calculated mean red blood cell lifespan of 16 days (normal in females: 94 ± 10 days). She was begun on prednisone, 60 mg/day. One week later her Hgb was 7.9 mg/dL, Hct 24%, reticulocytes 12.3%, and red blood cell mass 16.0 mL/kg. Her hepatic bilirubin clearance (CBR) was 0.56 mL/min/kg, her plasma unconjugated bilirubin concentration was 0.5 mg/dL, and her calculated mean red blood cell lifespan was 62 days. There was a disagreement among the consultants on her case. Based on her persistent anemia and reticulocytosis, a rheumatologist argued that the current therapy was ineffective and urged increasing her prednisone dose to 80 mg/day. The hematologist said that she was essentially cured and urged continuation of the current treatment with follow-up in 2 weeks. When the patient returned in 2 weeks, her data fully confirmed the hematologist's prediction. Her Hgb was 12.0 g/dL, Hct 36%,

reticulocytes 2.8%, and red blood cell mass 24.0 mL/kg. Plasma unconjugated bilirubin was 0.6 mg/dL. Which of the following test results led the hematologist to that correct conclusion?

- A. The Hgb
- B. The Hct
- C. The reticulocyte count
- D. The CBR
- E. The plasma unconjugated bilirubin concentration

Answer: E Hepatic bilirubin clearance (CBR), plasma bilirubin turnover (BRT), and plasma unconjugated bilirubin concentration (BR) are related by the formula: $BR \approx BRT / CBR$. In the present case, the plasma unconjugated bilirubin concentration fell by 76% during the first week of prednisone therapy, whereas CBR was virtually unchanged. These data meant that the fall in plasma bilirubin concentration must have resulted from a decrease in plasma bilirubin turnover, which, in fact, also declined by 75%. Because the major source of bilirubin is the dying red blood cell, the conclusion is that RBC death must have declined by approximately the same 75%, precisely accounting for the nearly four-fold increase in calculated red blood cell lifespan. Thus, the fall in bilirubin concentration accurately reflected the beneficial effects of steroids on red blood cell survival in this patient with autoimmune hemolysis. By contrast, the continued reticulocytosis during the first week of prednisone treatment reflected the bone marrow's attempt to heal the ongoing anemia, not to the hemolytic process per se.

3. A 36-year-old man with a history of injection drug use is discovered to have hepatitis C and HIV coinfection during a medical screening examination. He has no signs or symptoms of chronic liver disease or portal hypertension, nor is there a history of AIDS-defining illnesses. Laboratory studies reveal albumin 4.2 mg/dL, AST 76 IU/mL, ALT 113 IU/mL, total bilirubin 0.6 mg/dL, and CD4 cells 450 cells/ μ L. Both HCV RNA and HIV RNA are detectable by PCR assays. Antiretroviral therapy is initiated with a combination of medications that include atazanavir. Evaluation following the start of antiretroviral therapy discloses mild scleral icterus. Laboratory results obtained following the start of treatment revealed albumin 4.0 mg/dL, AST 81 IU/mL, ALT 145 IU/mL, total bilirubin 2.4 mg/dL, direct bilirubin 0.3 mg/dL and haptoglobin 150 mg/dL. Which of the following is the most appropriate next step with regard to the jaundice?

- A. Observation
- B. Liver ultrasonography
- C. Discontinuation of atazanavir
- D. Liver biopsy
- E. Magnetic resonance cholangiopacreatography

Answer: A Rates of HIV-HCV coinfection vary widely in populations but are highest in individuals with a history of injection drug use. The development of a mild indirect hyperbilirubinemia in the absence of evidence of hemolysis is strong evidence of Gilbert syndrome. Certain medications, including the antiretroviral protease inhibitor atazanavir, are inhibitors of UGT1A1 and also result in a mild, indirect hyperbilirubinemia similar to that seen in Gilbert syndrome. Atazanavir-associated hyperbilirubinemia may be more pronounced in individuals with Gilbert syndrome or with baseline hyperbilirubinemia from underlying liver disease. Although liver injury can occur with antiretroviral medications, there is no such factor in this case. Instead, the pattern is consistent with an acquired indirect hyperbilirubinemia related to atazanavir. No further diagnostic evaluation is warranted.

4. A 22-year-old woman is referred to your care for the evaluation of jaundice. She gives a history of episodic jaundice that is most pronounced around times of illness. On physical examination, she is well developed and healthy appearing. Scleral icterus is noted. The abdomen is soft, and there is neither shifting dullness nor organomegaly. Laboratory studies reveal hemoglobin 13 g/dL, platelets 225,000, alkaline phosphatase 95 IU/mL, AST 13 IU/mL, ALT 20 IU/mL, albumin 4.1 mg/dL, total bilirubin 2.4 mg/dL, direct bilirubin 1.5 mg/dL. Liver ultrasonography reveals cholelithiasis without gallbladder wall thickening. Which of the following is the next most appropriate diagnostic step?

- A. Cholecystectomy with intraoperative cholangiography
- B. Liver biopsy
- C. Mutation analysis of the ABC transporter *ATP8B1*
- D. Laboratory testing for antimitochondrial antibodies
- E. Measurement of urinary coproporphyrin isomers

Answer: E Heritable disorders of bilirubin metabolism should be considered in the setting of a mixed or predominately direct hyperbilirubinemia in the absence of evidence of cholestasis. Dubin-Johnson syndrome is an autosomal recessive disorder arising from mutations in the ATP-dependent canalicular organic anion transporter MPR2/cMOAT. The diagnosis of Dubin-Johnson syndrome can be established by the measurement of urinary coproporphyrin isomers; the coproporphyrin isomer 1 is generally greater than 80% of total coproporphyrin concentration. Although liver biopsy is not required nor necessary for the diagnosis, the liver in Dubin-Johnson is described as containing a dark pigment comprising polymerized epinephrine metabolites.

5. A 34-year-old Hispanic woman presents for the preoperative evaluation for cholecystectomy. For the past 3 months, she has experienced episodic, colicky, right upper quadrant pain. On examination, she is obese (BMI 35 kg/m²). She has no signs or symptoms of liver disease or portal hypertension. Laboratory evaluation reveals: ALT 44 IU/mL, AST 42 IU/mL, total bilirubin, alkaline phosphatase, and γ -glutamyl transpeptidase (GGT) are within the laboratory's reference range. Tests for chronic viral hepatitis, common genetic causes of chronic liver disease, and autoimmune liver disease are all negative. Her ferritin level is 400 ng/mL, and her transferrin saturation 27%. Liver ultrasonography reveals increased echogenicity of the liver and cholelithiasis without thickening of the gallbladder wall. In addition to cholecystectomy, which of the following options should be recommended?

- A. *Hfe* genotype
- B. Serologic studies for celiac disease
- C. Nucleic acid testing for viral hepatitis
- D. Intraoperative liver biopsy during cholecystectomy
- E. Treatment with vitamin E (d- α) 800 IU daily.

Answer: D Liver diseases are commonly associated with aminotransferase elevations 2 or greater times the upper limits of the reference range. In some individuals, however, ALT levels at or within the upper limits of the reference range may be observed with nonalcoholic fatty liver disease (NAFLD). Thus, in patients at risk for NAFLD, it is imperative that aminotransferases be interpreted in the context of the patient's history, physical examination, and other laboratory findings. The presence of obesity and modest elevations in the ferritin level (without an increase in transferrin saturation) are commonly seen in subjects with NAFLD. Although the ferritin level is elevated, the transferrin saturation is not, so hereditary hemochromatosis is unlikely. Intraoperative liver biopsy is a safe and effective tool for diagnosing NAFLD and assessing the extent of fibrosis.

1. Which of the following viruses can cause chronic hepatitis?

- A. Only hepatitis A virus
- B. Hepatitis B and C viruses
- C. Hepatitis B, C, and D viruses
- D. Hepatitis B, C, D, and E viruses
- E. Hepatitis A, B, C, D, and E viruses

Answer: D Hepatitis A virus never causes chronic infection and related liver disease. HBV infection becomes chronic in 95% of infants at birth and in less than 1% of adults. HCV infection becomes chronic in approximately 80% of cases. HDV infection rarely becomes chronic in cases of coinfection but almost systematically becomes chronic in case of superinfection in a chronic HBV carrier. HEV infection can become chronic in immunosuppressed patients.

2. Which of the following viruses are the main causes of hepatocellular carcinoma (primary liver cancer) worldwide?

- A. Only hepatitis A virus
- B. Hepatitis A and B viruses
- C. Hepatitis B and C viruses
- D. Hepatitis A and C viruses
- E. Hepatitis C and E viruses

Answer: C Because of the prevalence of their chronic infection, their carcinogenic properties, and their ability to induce cirrhosis after many years of infection, both HBV and HCV currently are the main causes of hepatocellular carcinoma, with a predominance of HBV in developing regions and HCV in industrialized regions.

3. Which of the following sentences about hepatitis E virus (HEV) is true?

- A. HEV infections are always self-limiting.
- B. Chronic HEV infection occurs exclusively in immunosuppressed patients.
- C. HEV infection cannot be diagnosed biologically.
- D. The treatment of chronic HEV infection is based on antiviral molecules active only against HEV.
- E. HEV RNA is never detected in blood.

Answer: B HEV infection is generally self-limiting but may become chronic in immunosuppressed patients. It is diagnosed by the presence of anti-HEV antibodies, in particular anti-HEV IgM at the acute stage, although HEV RNA can be detected in feces and blood. Treatment is based on the use of pegylated IFN- α and/or ribavirin, nonspecific antiviral molecules that are also used in the treatment of chronic hepatitis B or C.

1. A 24-year-old woman is brought to the emergency department by her family because of altered mental status. She is rousable but drowsy, with normal vital signs except for tachycardia. Initial testing shows AST 10,200 IU/L, ALT 8,100 IU/L, INR 3.2, T bilirubin 3.7 mg/dL. The most plausible explanation for this scenario is:

- A. Alprazolam (Xanax) overdose.
- B. Alcohol binge drinking.
- C. Aspirin overdose.
- D. Acetaminophen overdose.
- E. Methyl alcohol ingestion.

Answer: D Although drowsiness would follow alprazolam and possibly an alcoholic binge, only acetaminophen is associated with very high aminotransferases. Approximately 75% of acetaminophen overdoses occur in women.

2. The proper course of treatment for this patient would be:

- A. Gastric lavage.
- B. Normal saline at 250 mL/hour.
- C. Syrup of ipecac.
- D. Narcan by injection.
- E. Intravenous *N*-acetylcysteine.

Answer: E *N*-Acetylcysteine is a sulfhydryl donor that repletes glutathione and is effective in preventing liver injury when given early in acetaminophen overdose. Even after severe liver damage has occurred, it is still likely to be of some benefit.

3. A college student who is trying out for the wrestling team is seen for new-onset itching and jaundice. The most likely cause would be:

- A. Hepatitis A.
- B. Hepatitis D.
- C. Anabolic steroid use.
- D. Hepatitis E.
- E. Hepatitis C.

Answer: C Body-building supplements contain androgenic compounds highly associated with cholestatic liver disease, which is usually self-limited but very slow to resolve.

4. A 49-year-old truck driver with a body mass index of 42 is evaluated for life insurance. His cholesterol level is 285 mg/dL. He complains of right upper quadrant pain, and his abdominal ultrasound reveals a fatty liver. His AST is 42 IU/L, ALT is 34 IU/L. He should be considered for which of the following treatments?

- A. Phen-phen for weight reduction
- B. Herbal weight loss product
- C. Lovastatin 40 mg/day
- D. Daily aspirin 81 mg
- E. Support stockings

Answer: C Lovastatin will deal with his hypercholesterolemia. He also needs exercise and dietary programs to help lose weight.

5. A 42-year-old woman is found incidentally to have multiple masses in her liver, but she is totally asymptomatic. Biopsy of one of the masses discloses an hepatic adenoma. Which of her medications should be discontinued at this time?

- A. Oral contraceptive
- B. Metformin
- C. Lisinopril
- D. Hydrochlorothiazide
- E. Alprazolam

Answer: A Oral contraceptives, particularly after prolonged use, can be associated with hepatic adenomas. These adenomas regress but must be watched closely over time.

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ALCOHOLIC AND NONALCOHOLIC STEATOHEPATITIS

1. A 17-year-old adolescent boy presents with right upper quadrant discomfort of 3 to 4 months in duration. This pain is constant and is dull in nature. He consumes no alcohol. He has a long-standing history of type 1 diabetes, for which he takes subcutaneous insulin twice daily. Physical examination reveals a relatively thin individual with tender hepatomegaly. His blood test results were positive for elevated alanine aminotransferase (82 U/L; normal, <45 U/L), blood glucose (181 mg/dL; normal, <125 mg/dL), and hemoglobin A_{1c} (9%; normal, <7%). A liver ultrasound examination revealed increased echogenicity. Which is the likely diagnosis for this patient's abdominal discomfort, elevated alanine aminotransferase level, and tender hepatomegaly?

- A. Nonalcoholic fatty liver disease
- B. Glycogen hepatopathy
- C. Wilson disease
- D. Hemochromatosis
- E. Glycogen storage disorder

Answer: B Tender hepatomegaly, elevated alanine aminotransferase level, and echogenic liver by ultrasound evaluation are suggestive of some form of infiltrative liver disorder. In type 1 diabetics, especially those with poorly controlled blood glucose levels, there is risk of glycogen hepatopathy, which may be manifested with abdominal discomfort, hepatomegaly, and elevated liver test results. Glycogen accumulation also enhances echogenicity on ultrasound examination and may mimic fatty liver. One must keep in mind that type 1 diabetes is rarely if ever associated with nonalcoholic fatty liver disease. It is believed that hyperinsulinemia is needed for development of nonalcoholic fatty liver disease.

2. A 46-year-old woman presents with 3 weeks' duration of fatigue, anorexia, low-grade fever, and jaundice. She is a heavy drinker and has been consuming more than 7 drinks of vodka each night for the previous 5 years. She is otherwise healthy and is not taking any medications. Physical examination reveals an emaciated woman with deep scleral icterus, peripheral muscle wasting, tender hepatomegaly, and pedal edema. Laboratory test results show macrocytic anemia, mild leukocytosis, elevated aminotransferase levels, and direct bilirubinemia. Which of the following treatments is not a suitable treatment option for this individual?

- A. Alcohol abstinence
- B. Prednisolone
- C. N-Acetylcysteine
- D. Liver transplantation
- E. Enteral nutrition

Answer: D On the basis of the clinical picture, the most likely diagnosis for this individual's condition is acute alcoholic hepatitis. Liver transplantation is not a suitable treatment option for acute alcoholic

hepatitis in individuals who are actively consuming alcohol. Most transplant centers require up to 6 months of total abstinence and some form of behavioral therapy for underlying alcoholism. In eligible patients, 28 days of oral prednisolone improves short-term survival in individuals with acute alcoholic hepatitis. Similarly, some previous clinical investigations have shown promising results for *N*-acetylcysteine and enteral nutrition.

3. A 37-year-old morbidly obese man is noted to have an echogenic liver incidentally when he had an abdominal ultrasound examination performed for his hematuria. He has no right upper quadrant pain. He rarely consumes alcohol and takes no medications. His physical examination is essentially unremarkable except for morbid obesity with a body mass index of 42 kg/m². Blood test results show mildly elevated aminotransferase levels but otherwise are within normal range. Your likely diagnosis is nonalcoholic fatty liver disease (NAFLD), and you recommend weight loss. Which of the following best represents his liver condition?
- A. NAFLD is a rare condition, and its incidence has remained relatively steady during the last decade.
 - B. Type 2 diabetes, obesity, dyslipidemia, and metabolic syndrome are the major risk factors for NAFLD.
 - C. Hyperthyroidism is a common cause of NAFLD.
 - D. Sleep disturbance is rare in NAFLD.
 - E. This condition can be ignored because it is rarely of any clinical significance.

Answer: B Hypothyroidism, hypopituitarism, hypogonadism, polycystic ovary syndrome, and obstructive sleep disorders are emerging risk factors for NAFLD. Although hyperthyroidism is associated with liver test abnormalities, it is not known to be associated with fatty liver disease. In fact, thyroid hormone analogues may improve hepatic steatosis, although they may carry significant adverse events and are not a recommended treatment. Clearly, the incidence of NAFLD is increasing because of the increasing prevalence of obesity and related comorbid conditions, and it is now one of the most common causes of cirrhosis, liver failure, and liver cancer. Therefore, it cannot be ignored as clinically insignificant.

4. A 46-year-old woman presents with chronically elevated liver enzymes and mild hepatomegaly. She has type 2 diabetes, which is diet controlled, and has dyslipidemia, which is managed with a low-dose statin. She denies significant alcohol consumption. Her liver biopsy showed 30% hepatic steatosis with ballooned hepatocytes and mild sinusoidal fibrosis. Your clinical and histologic diagnosis is nonalcoholic steatohepatitis. Which of the following treatments is not a suitable option for her?
- A. Weight loss
 - B. Pioglitazone
 - C. Vitamin E
 - D. Ursodeoxycholic acid
 - E. Pentoxifylline

Answer: D Weight loss is the first-line treatment option for both NAFLD and NASH. Loss of 3 to 5% of body weight will improve hepatic steatosis, whereas a loss of 7 to 10% is needed to see an improvement in steatohepatitis. Calorie restriction and physical exercise are advised to achieve the desired weight loss in individuals with NAFLD and NASH. When such measures are not achieved, therapy with agents such as pioglitazone, vitamin E, and pentoxifylline can be considered. In clinical studies, these compounds have shown therapeutic efficacy in various subgroups of patients. Ursodeoxycholic acid, a medication used to treat primary biliary cirrhosis, has been tested in individuals with NASH but has not proved to be effective. Metformin is not effective for improving liver histology findings in NASH and therefore should not be used for this purpose.

1. A 55-year-old man with chronic hepatitis C complains of fatigue. On physical examination, he has vascular spiders, palmar erythema, and a palpable left lobe of his liver. He has no ascites or asterixis. Laboratory analysis demonstrates aspartate aminotransferase 100, alanine aminotransferase 67, alkaline phosphatase 145, and platelet count of 120,000. Abdominal computed tomography (CT) scan shows a nodular liver contour, portosystemic collaterals, but no masses. Which of the following would you recommend as the next step?

- A. Liver biopsy
- B. Upper endoscopy
- C. Start nonselective β -blockers
- D. Start spironolactone
- E. Magnetic resonance imaging of the liver

Answer: B Although the “gold standard” in the diagnosis of cirrhosis is liver biopsy, this procedure is not necessary when clinical, laboratory, and imaging results are sufficient to establish the diagnosis. In the setting of chronic liver disease, a palpable left lobe of the liver is almost diagnostic of cirrhosis. The most sensitive and specific laboratory finding suggestive of cirrhosis in the setting of chronic liver disease is a low platelet count ($<150,000/\mu\text{L}$) due to portal hypertension and hypersplenism.¹ Confirmatory imaging tests include ultrasound, CT, and magnetic resonance imaging. Findings consistent with cirrhosis include a nodular liver surface, a small liver with or without left or caudate lobe hypertrophy, splenomegaly, and especially the identification of intra-abdominal collaterals, which are indicative of portal hypertension. A liver biopsy is not required if these findings are present. Any patient with newly diagnosed cirrhosis should undergo upper endoscopy to investigate the presence and size of gastroesophageal varices.² β -Blockers should be initiated in patients with medium or large varices or in patients with high-risk small varices (i.e., those present in a Child class C patient or with red wale marks). β -Blockers are not useful in patients without varices and are associated with significant adverse events.³ Studies have not shown diuretics to be useful in patients with compensated cirrhosis. In the absence of masses on CT scan or ultrasound, performing a magnetic resonance imaging study is unnecessary.

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2. Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology.* 2007;46:922-938.
3. Groszmann RJ, Garcia-Tsao G, Bosch J, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med.* 2005;353: 2254-2261.

2. A 69-year-old obese, diabetic man with biopsy-proven compensated cirrhosis and without a prior history of variceal hemorrhage has large esophageal varices on a screening endoscopy study. Which of the following medications would you recommend at this point?

- A. No specific medication
- B. Metoprolol
- C. Nadolol
- D. Spironolactone
- E. Pantoprazole

Answer: C Nonselective β -blockers are the treatment of choice for the primary prevention of variceal bleeding.¹ In patients with large varices, the 2-year rate of first variceal hemorrhage is significantly lower in patients receiving nonselective β -blockers (15%) compared with those receiving no specific medication. β_1 -Specific blockers (atenolol, metoprolol) are not as effective as nonselective (β_1 and β_2) β -blockers (nadolol or propranolol) or a nonselective β -blocker with vasodilating properties (carvedilol)^{2,3} because the most important portal pressure-reducing effect results from β_2 -blockade. Spironolactone is a diuretic that may reduce portal pressure but has not been shown to prevent first

variceal hemorrhage. Although there appears to be a benefit in blocking gastric acid with proton pump inhibitors for the reduction of post-ligation ulcers and bleeding, there is no benefit in preventing a first variceal bleed.

1. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. *Semin Liver Dis.* 1999;19: 475-505.
2. Hillon P, Lebrec D, Munoz C, et al. Comparison of the effects of a cardioselective and a nonselective beta-blocker on portal hypertension in patients with cirrhosis. *Hepatology.* 1982;2:528-531.
3. Mills PR, Rae AP, Farah DA, et al. Comparison of three adrenoreceptor blocking agents in patients with cirrhosis and portal hypertension. *Gut.* 1984;25:73-78.

3. A 64-year-old obese man presents for evaluation of new ascites and peripheral edema. He is a heavy smoker and typically drinks two to four alcoholic beverages daily, but he has no history of liver disease. Physical examination reveals decreased breath sounds, moderate ascites, and peripheral edema but no other abnormalities. Laboratory tests reveal a total bilirubin 1.2 mg/dL, aspartate aminotransferase 37 IU/mL, alanine aminotransferase 35 IU/mL, albumin 3.7 g/dL, and international normalized ratio of 1.4. Paracentesis discloses clear yellow fluid with the following characteristics: total protein 3.5 g/dL, albumin 1.7 g/dL, white blood cells 640/ μ L (12% neutrophils). Which one of the following is the most appropriate action?

- A. Begin intravenous cefotaxime and await ascites culture results
- B. Perform a liver biopsy
- C. Obtain serum B-type natriuretic peptide and perform cardiac echocardiography
- D. Perform an abdominal CT scan to investigate peritoneal malignant disease
- E. Begin therapy for tuberculosis

Answer: C This patient without documented chronic liver disease has ascites with a high serum-ascites albumin gradient (>1.1 g/dL), indicating ascites that is secondary to hepatic sinusoidal hypertension.¹ The fluid also has a high protein content (>2.5 g/dL) indicative of normal "leaky" sinusoids, so the problem is unlikely to be in the liver. A liver biopsy would not be the most indicated test. In this clinical setting, the most likely possibility is right-sided heart failure, which should be evaluated, initially with an echocardiogram. A high serum B-type natriuretic peptide has a high diagnostic accuracy in the diagnosis of ascites due to heart failure.² Although the ascites total white blood cell count is somewhat elevated, the fluid contains only 77 neutrophils (640×0.12), and therefore it is not consistent with bacterial peritonitis, which is based on more than 250 neutrophils/ μ L.³ In peritoneal causes of ascites (carcinomatosis, tuberculosis), the ascites protein is high and the serum-to-ascites albumin gradient is low ($<1/1$ g/dL) because fluid formation does not result from sinusoidal hypertension.

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2. Farias AQ, Silvestre OM, Garcia-Tsao G, et al. Serum B-type natriuretic peptide in the initial workup of patients with new onset ascites: a diagnostic accuracy study. *Hepatology.* 2014;59:1043-1051.
3. Rimola A, Garcia-Tsao G, Navasa M, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. *J Hepatol.* 2000;32:142-153.

4. A 53-year-old woman with cirrhosis secondary to primary biliary cirrhosis presents with 2 weeks of weight gain and an increase in abdominal girth. On physical examination, she has gained 8 pounds, and she has a modestly distended abdomen with flank dullness and shifting dullness. She does not have asterixis. Her laboratory tests include creatinine 0.8, blood urea nitrogen 24, Na 136, K 3.5. Analysis of her ascitic fluid is compatible with cirrhotic ascites, without any evidence of spontaneous bacterial peritonitis. An ultrasound examination shows no hepatic masses. Appropriate management at this point should be

- A. Large-volume paracentesis
- B. Salt and water restriction alone

C. Transjugular intrahepatic portosystemic shunt (TIPS)

D. Spironolactone

E. Intravenous furosemide

Answer: D The patient has the new onset of uncomplicated, nontense ascites. The mainstay of therapy is sodium restriction and diuretics. Water restriction is not indicated unless her serum sodium concentration is below 125 mEq/L.¹ The most effective diuretic is spironolactone, which should be initiated alone at a dose of 100 mg once daily in the morning, particularly in patients with modest ascites. Furosemide is not as effective as spironolactone² because sodium that is not reabsorbed in the loop of Henle is taken up at the distal and collecting tubules as a result of the hyperaldosteronism that is present in most patients with cirrhosis and ascites. Therefore, furosemide should not be used as the sole agent in the treatment of cirrhotic ascites and should not be used intravenously. Large-volume paracentesis is indicated to decrease discomfort in patients with tense ascites and is first-line therapy for patients with refractory ascites. TIPS placement is second-line therapy for patients with refractory ascites.¹

1. Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology*. 2013;57:1651-1653.

2. Perez-Ayuso RM, Arroyo V, Planas R, et al. Randomized comparative study of efficacy of furosemide versus spironolactone in nonazotemic cirrhosis with ascites. Relationship between the diuretic response and the activity of the renin-aldosterone system. *Gastroenterology*. 1983;84:961-968.

5. A 48-year-old man with chronic hepatitis C virus infection, cirrhosis, and ascites presents with 2 days of confusion. He denies fever, chills, hematemesis, or melena. On physical examination, his temperature is 35.5° C, blood pressure 90/60, heart rate 100 beats per minute, respiratory rate 30/minute. He is confused and agitated, and asterixis is present. His abdomen has tense ascites but is nontender, and his stool is negative for blood. His laboratory tests include white blood cell 8.6, creatinine 2.1 (previously 0.8), and bilirubin 7.7 (previously 2.3). He is making only small amounts of urine, but his urinalysis is normal. Which of the following is the most appropriate test?

A. Diagnostic paracentesis and blood cultures

B. Large-volume paracentesis

C. Upper endoscopy

D. Brain CT

E. Renal ultrasound

Answer: A The presence of unexplained encephalopathy or deterioration in renal function in a patient with ascites should always raise the suspicion of spontaneous bacterial peritonitis (SBP), so therefore a diagnostic paracentesis should always be performed in this setting.¹ The ascites culture is negative in about 40% of patients with SBP, so ascites and blood cultures should be performed whenever SBP is suspected. In this patient, blood cultures are particularly important because he presents with evidence of systemic inflammatory response system (hypothermia, tachycardia, and tachypnea) and jaundice and therefore may be septic. Large-volume paracentesis in this setting could theoretically lead to further deterioration in renal function and should be avoided. There is no evidence of gastrointestinal bleeding, so endoscopy is not indicated. Brain scan is not an initial test in a cirrhotic patient with encephalopathy unless there is a history of trauma or other causes of encephalopathy are suspected. A renal ultrasound study is a low-yield test because obstruction is an unlikely cause of his decompensation.

1. Rimola A, Garcia-Tsao G, Navasa M, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. *J Hepatol*. 2000;32:142-153.

1. A 50-year-old male liver transplant recipient comes to your office with community-acquired pneumonia, for which he had been prescribed erythromycin 7 days ago by an emergency department physician. His maintenance immunosuppression is tacrolimus and mycophenolate mofetil. He is now confused, and his laboratory tests reveal Na 135, K 6.2, HCO₃ 15, Cl 108, blood urea nitrogen 45, creatinine 4.1. The results of his complete blood count and the rest of the chemistry profile are normal. A computed tomography scan of the brain is unremarkable. The most likely cause of this patient's clinical presentation is

- A. Viral meningitis
- B. Urinary tract infection
- C. Tacrolimus toxicity
- D. Mycophenolate mofetil toxicity
- E. Erythromycin toxicity

Answer: C A key to appropriate management of the liver transplant recipient is an understanding of potential drug-drug interactions. Calcineurin and mTOR inhibitors are cornerstones of maintenance immunosuppression in most liver recipients. These drugs are processed by P-glycoprotein and metabolized by CYP3A4, both of which are key drug disposition pathways located in intestinal epithelial cells, hepatocytes, and renal tubular cells. Erythromycin inhibits CYP3A4, thereby blocking the metabolism of tacrolimus and leading to high tacrolimus levels and tacrolimus renal and neurologic toxicity. Physicians must check for any drug-drug interactions before prescribing medications to liver transplant recipients who are taking immunosuppressive medications.

2. A 62-year-old woman who received a liver transplant 5 years ago comes for a routine physical examination. She has a body mass index of 32 kg/ m², blood pressure (BP) 165/105, total cholesterol 285 mg/dL (low-density lipoprotein 205 mg/dL), triglycerides 305 mg/dL, and fasting blood glucose of 165 mg/dL. Her current immunosuppression regimen is cyclosporine and prednisone. You notify her transplant center, and they switch her immunosuppression to low-dose tacrolimus and mycophenolate mofetil. The expected outcomes of the change in immunosuppression are

- A. Weight loss, lower BP, improved lipids, improved insulin sensitivity
- B. Weight gain, lower BP, improved lipids, improved insulin sensitivity
- C. Weight loss, higher BP, improved lipids, improved insulin sensitivity
- D. Weight loss, lower BP, higher lipids, improved insulin sensitivity
- E. Weight loss, lower BP, improved lipids, worsened insulin resistance

Answer: A Each immunosuppressive medication has a characteristic pattern of side effects. Most are manageable by dose reduction or changing the immunosuppressive prescription. In this case, both cyclosporine and prednisone contributed to the constellation of obesity, hypertension, dyslipidemia, and glucose intolerance. Mycophenolate mofetil does not have these side effects, and low-dose tacrolimus is less likely than cyclosporine to cause obesity, dyslipidemia, or glucose intolerance.

3. A 47-year-old woman underwent liver transplantation for autoimmune hepatitis 5 years ago. After transplantation, she experienced steroid-refractory rejection, which was treated with antilymphocyte globulin, and cytomegalovirus hepatitis, which was treated with intravenous ganciclovir. She now presents with fever, leukopenia, anemia, and lymphadenopathy. Viral, bacterial, and fungal cultures are negative. Epstein-Barr virus serology indicates past exposure, but Epstein-Barr virus DNA is negative. Lymph node biopsy is likely to demonstrate

- A. Mycobacteria
- B. Epstein-Barr Virus
- C. Cytomegalovirus
- D. Fungi
- E. CD20-positive lymphocytes

Answer: E Risk factors for post-transplantation lymphoproliferative disease (PTLD) include primary Epstein-Barr virus infection, cytomegalovirus disease, cytomegalovirus donor-recipient mismatch, and augmented immunosuppression, especially antilymphocyte globulin. The association of PTLD and Epstein-Barr virus is variable in adult liver transplant recipients; later onset PTLD is less likely to be associated with Epstein-Barr virus activation or infection. Fever, cytopenias, and lymphadenopathy are the key clinical features. Initial treatment is a reduction in immunosuppression. Monoclonal anti-CD20 antibodies and chemoradiation treatments may be required. Antiviral therapy is ineffective.

Ch / 155 **DISEASES OF THE GALLBLADDER AND BILE DUCTS**

1. A 55-year-old woman is found to have several large calcifications in the right upper quadrant on plain radiographs of her spine, performed as part of her routine chiropractic examination. She denies abdominal pain and has normal serum liver test results. She has diabetes mellitus but no other significant comorbidities. Subsequent abdominal ultrasound reveals a 3.8-cm gallbladder stone, three smaller stones each less than 10 mm in diameter, a normal gallbladder wall, and a nondilated bile duct. The *most appropriate* next step in the management of this patient is

- A. Magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) for further evaluation of her biliary tree
- B. Oral dissolution therapy with ursodeoxycholic acid
- C. Surgical consultation for elective laparoscopic cholecystectomy
- D. Extracorporeal shock wave lithotripsy
- E. Continue a conservative watch-and-wait approach, with surveillance ultrasound in 12 months

Answer: C As discussed for asymptomatic gallstones, gallbladder stones larger than 3 cm are associated with an increased incidence of acute cholecystitis, and there is a 10-fold increased risk of gallbladder cancer. Prophylactic cholecystectomy is recommended in this scenario. MRI/MRCP may be considered, but it is unlikely to add additional information in this patient because significant bile duct disease is less likely in the setting of a nondilated bile duct on ultrasound, with normal liver test results. The nonoperative methods listed (ursodeoxycholic acid, extracorporeal shock wave lithotripsy) are not options in patients with gallbladder stones of this size. A conservative watch-and-wait approach may be advocated by some in this asymptomatic patient, but given the increased cancer risk and her lack of significant comorbidities, surgery is the better option here. Furthermore, there is no evidence to support surveillance ultrasound in 12 months.

2. A 44-year-old woman with a history of recurrent urinary tract infections undergoes abdominal/renal ultrasound for further evaluation. She previously underwent laparoscopic cholecystectomy for gallbladder stones 20 years ago. Ultrasound reveals normal kidneys without hydronephrosis, but an incidental single 8-mm shadow suggesting a common bile duct stone is seen. The bile duct is 11 mm in diameter. She denies upper abdominal pain but has noted nausea and dark urine recently, which she has attributed to a recurrent urinary tract infection. She also notes diffuse pruritus. Her serum liver test results are as follows: aspartate transaminase 78 IU/L (normal, <40 IU/L), alanine transaminase 95 IU/L (<45 IU/L), alkaline phosphatase 235 IU/L (<125 IU/L), bilirubin 3.2 mg/dL (<1.0 mg/dL). Which of the following statements is the *most correct*?

- A. Magnetic resonance cholangiopancreatography (MRCP) should be performed to confirm the finding of a bile duct stone, given the poor specificity of transabdominal ultrasound for detection of choledocholithiasis.
- B. The bile duct stone is most likely to be a cholesterol stone.
- C. In the absence of abdominal pain, a watch-and-wait approach is justified in this scenario.
- D. Proceed directly to endoscopic retrograde cholangiopancreatography (ERCP) for attempted bile duct stone removal.
- E. Perform a surgical exploration.

Answer: D Although transabdominal ultrasound has a low sensitivity for detection of common bile duct stones, its specificity is more than 90% in most series. MRCP is unnecessary in this case because the patient also has elevated liver test values and biliary dilation. Choledocholithiasis occurring 20 years after cholecystectomy probably represents a primary bile duct stone, which is likely to be a brown pigment stone rather than a cholesterol stone. Given the potential for severe, even life-threatening complications of bile duct stones (cholangitis, pancreatitis), a watch-and-wait approach is not recommended. Proceeding with ERCP and stone removal is the most appropriate next step in this scenario.

3. Regarding primary sclerosing cholangitis (PSC), which of the following statements is *true*?

- A. Women outnumber men in a 2 : 1 ratio.
- B. A liver biopsy demonstrating characteristic findings is necessary to establish the diagnosis of PSC in all affected patients.
- C. Ursodeoxycholic acid is the only medical therapy that has been shown to slow the progression of PSC.
- D. The risk for development of cholangiocarcinoma increases with the duration of the disease.
- E. Current guidelines suggest that bone densitometry be performed in all PSC patients at diagnosis and every 2 to 3 years thereafter.

Answer: E Affected PSC patients are at risk for hepatic osteodystrophy, a metabolic bone disease that may be seen in chronic liver disease. The American Association for the Study of Liver Diseases (AASLD) has suggested that bone densitometry be performed to screen for this disorder. PSC is seen more commonly in men than in women in a 2 : 1 ratio. Cholangiography is necessary to establish the diagnosis of PSC because liver biopsy findings are nonspecific. Only in patients with “small-duct PSC,” in which cholangiography is normal, may the liver biopsy suggest the diagnosis in association with other associated features (e.g., presence of inflammatory bowel disease, elevated alkaline phosphatase). No medical therapy has been shown to slow the progression of PSC, and recent AASLD guidelines do not support the routine use of ursodeoxycholic acid in these patients. Interestingly, there is an inverse relationship between incidence of cholangiocarcinoma and duration of PSC; PSC patients who have had the disease for a shorter time appear to be at increased risk for the development of this complication.

4. A 35-year-old woman presents to you for evaluation of a 6-month history of episodic, postprandial right upper quadrant pain. Her pain is identical to pain that previously responded to cholecystectomy 4 years ago for a functional gallbladder disorder. No gallbladder stones were identified at surgery. Aspartate transaminase and alanine transaminase were both found to be two to three times elevated during two recent emergency department visits but are normal on days when she is pain free. Alkaline phosphatase, bilirubin, amylase, and lipase levels are repeatedly normal. You obtain MRI/MRCP, which reveals a normal pancreas and biliary tree without intraductal filling defects or duct dilation. Findings on upper endoscopy and endoscopic ultrasound are normal. She continues to work full-time, without days missed from work, need for hospitalization, or use of narcotics. Which of the following statements is *correct*?

- A. A common bile duct stone is the most likely diagnosis.
- B. A liver biopsy is recommended as the next investigation.
- C. She may have type III sphincter of Oddi dysfunction.
- D. A trial of nifedipine or other antispasmodic is suggested before proceeding with ERCP.
- E. This patient is at low-risk for the development of post-ERCP pancreatitis.

Answer: D Bile duct stones can occur after cholecystectomy but are rarely found in a patient who did not have gallbladder stones at cholecystectomy, especially in the absence of factors that increase the likelihood of bile stasis (see Bile Duct Stones, Pathobiology). Furthermore, normal findings on MRCP and endoscopic ultrasound make this diagnosis much less likely. Given the elevated liver test values associated with abdominal pain, but not during normal pain-free intervals, a biliary etiology is more

likely than hepatocellular disease. Liver biopsy, therefore, is less likely to be helpful in the diagnostic evaluation of this patient. Biliary-type pain associated with elevated liver test values during attacks of pain and a nondilated bile duct on abdominal imaging defines type II sphincter of Oddi dysfunction. Medical trials with nonspecific antispasmodics or smooth muscle relaxants (e.g., calcium-channel blockers) should be considered in less severely symptomatic patients before proceeding with ERCP and sphincter of Oddi manometry as patients with suspected sphincter of Oddi dysfunction are at high risk for post-ERCP pancreatitis.

5. A 44-year-old woman with a remote history of alcohol abuse is brought to her local emergency department for evaluation after her family noted that her eyes and skin were yellow. She has been abstinent from alcohol for 15 years. She notes mild pruritus but is otherwise asymptomatic and has lost no weight. She previously had complained of episodic abdominal pain and was found to have a decreased gallbladder ejection fraction, leading to laparoscopic cholecystectomy 6 months earlier. Ultrasound did not reveal gallbladder stones. Her pain completely resolved postoperatively. Laboratory tests in the emergency department reveal a normal complete blood count, serum bilirubin 6.0 mg/dL (normal, <1 mg/dL), alkaline phosphatase 722 IU/L (<125 IU/L), aspartate transaminase 93 IU/L (<45 IU/L), alanine transaminase 101 IU/L (<40 IU/L), amylase 64 IU/L (<125 IU/L), and CA19-9 367 U/mL (<37 U/mL). A computed tomography scan with intravenous administration of contrast material reveals dilated intrahepatic bile ducts proximal to the mid- hepatic duct, adjacent to the cholecystectomy clips, as well as a normal distal bile duct and pancreas, without stones or mass identified. Her pancreatic duct is normal. Which of the following statements is *true*?
- A. Choledocholithiasis is the most likely diagnosis.
 - B. The elevated CA19-9 suggests that the most likely diagnosis is cholangiocarcinoma.
 - C. MRI/MRCP would be expected to identify a type I choledochal cyst in this scenario.
 - D. The presentation 6 months after cholecystectomy is consistent with a postoperative bile duct injury.
 - E. Your most likely diagnosis is a benign biliary stricture from chronic pancreatitis.

Answer: D Bile duct injuries after laparoscopic cholecystectomy may be manifested in the immediate postoperative period (e.g., bile duct transection or when a surgical clip is placed over the common bile duct) or delayed, when thermal or ischemic injury may result in a biliary stricture. Ischemic injuries most commonly occur within a few months of surgery but may be manifested longer than 1 year postoperatively. Although primary bile duct stones may occur after cholecystectomy, they are very unlikely when gallbladder stones are not identified before surgery, as in this case. An elevated CA19-9 may be seen in any tumor that causes biliary obstruction (not specific to cholangiocarcinoma) as well as in benign obstructing lesions (bile duct stones, primary sclerosing cholangitis). The computed tomography findings of biliary dilation adjacent to the surgical clips and a nondilated distal bile duct suggest an obstructing lesion in the proximal bile duct (e.g., stricture, stone), not a type I choledochal cyst. A patient with a history of alcohol abuse might present with cholestatic liver test results and painless jaundice from a biliary stricture secondary to chronic pancreatitis, but such a complication would be less likely in a patient who has been abstinent for 15 years. Furthermore, cross-sectional imaging or cholangiography would be expected to reveal a distal biliary stricture within the head of the pancreas or perhaps with a dilated bile duct proximally, not the imaging findings described in this case.

1. A 72-year-old woman presents with gradual onset of digital paresthesia and difficulty with fine movement of the hands. More recently, she has noticed an electrical sensation running down her trunk and into her limbs when she bends her head forward. She is found to have a hemoglobin concentration of 9.8 g/dL and a mean cell volume of 107 fL. A blood film shows macrocytes, oval macrocytes, and hypersegmented neutrophils. Which of the following is the most likely diagnosis?

- A. Neuroacanthocytosis
- B. Vitamin B12 deficiency
- C. Folic acid deficiency
- D. Alcoholic liver disease
- E. Copper deficiency

Answer: B The patient has described the features of peripheral neuropathy and Lhermitte syndrome. These neurologic features in a patient with macrocytic anemia and hypersegmented neutrophils are indicative of vitamin B12 deficiency causing megaloblastic anemia, peripheral neuropathy, and sub-acute combined degeneration of the spinal cord (Chapter 164). (Larkman N, Hulson O, Gilhooly M. Picture quiz: a man with tingling fingers. *BMJ*. 2013;346:37-38.)

2. A 67-year-old man presents with right heart failure and extensive bruising. The cardiac silhouette is normal on chest radiography. Electrocardiography shows reduced voltage of QRS complexes. Coagulation screen shows prolongation of the prothrombin time and activated partial thromboplastin time. A full blood count is normal apart from a slight increase of the platelet count to $487 \times 10^9/L$. A blood film shows Howell-Jolly bodies, target cells, occasional acanthocytes, and platelet anisocytosis. There is no relevant previous medical history. Which of the following is the most likely diagnosis?

- A. Essential thrombocythemia
- B. Hypothyroidism
- C. AL (light-chain associated) amyloidosis
- D. Acquired hemophilia
- E. Disseminated intravascular coagulation

Answer: C The blood film features are those of hyposplenism, which also provides an explanation for the slight increase in the platelet count. The hyposplenism is the result of extensive amyloid deposition in the spleen. AL amyloidosis causes a variety of coagulation abnormalities, including acquired factor X deficiency, which could explain the prolonged prothrombin and activated partial thromboplastin times (Chapter 188). Acquired hemophilia would not explain the hyposplenism. (Gatt ME, Palladini G. Light chain amyloidosis 2012: a new era. *Br J Haematol*. 2013;160:582-598; and Gillmore JD, Wechalekar A, Bird J, et al. Guidelines on the diagnosis and investigation of AL amyloidosis. *Br J Haematol*. 2015;168:207-218.)

3. A young Greek woman presents to the emergency department because of the sudden onset of jaundice and fatigue. She has just returned from a brief trip to Greece for a family wedding. She is taking no medications. She is noted to be pale and has tachycardia. Her hemoglobin concentration is 8.7 g/dL and mean corpuscular volume is 109 fL. Reticulocyte count is increased to $280 \times 10^9/L$. Bilirubin is elevated and is found to be mainly unconjugated. Her blood film confirms marked anemia and shows polychromatic macrocytes, irregularly contracted cells, hemighosts (blister cells), and a few ghost cells. An assay for glucose-6-phosphate dehydrogenase is normal. Which of the following is the most likely diagnosis?

- A. Acute liver failure
- B. Autoimmune hemolytic anemia
- C. Glucose-6-phosphate dehydrogenase deficiency
- D. Hereditary spherocytosis
- E. Pyruvate kinase deficiency

Answer: C Unconjugated hyperbilirubinemia does not suggest acute liver failure. The blood film features are those of oxidant-induced hemolysis, and a diagnosis of glucose-6-phosphate dehydrogenase (G6PD) deficiency must therefore be considered. The blood film features are not consistent with the other types of hemolytic anemia listed. Most patients with acute hemolysis due to G6PD deficiency are men because this is an X-linked condition. However, hemolysis can occur in women because a proportion of red cells will be deficient. If there is marked lysis, hemolysis may be severe. The G6PD assay is likely to be normal because the remaining red cells are not deficient and the G6PD concentration will be increased by the presence of reticulocytes. In this circumstance, the blood film is very important in suggesting the right diagnosis. A dietary history should be taken. It is possible that the patient has recently eaten broad beans (Chapter 161). (Bain BJ. Sudden onset of jaundice in a Sardinian man. *Am J Hematol*. 2008;83:810; Bain BJ. A ghostly presence. *Am J Hematol*. 2010;85:271.)

4. A 35-year-old pregnant woman complains of severe fatigue and swollen ankles. Her blood count shows the following: red blood cells, $4.22 \times 10^{12}/L$; hemoglobin concentration, 7 g/dL; hematocrit, 0.29 L/L; mean corpuscular volume, 67 fL; mean corpuscular hemoglobin, 16.6 pg; mean corpuscular hemoglobin concentration, 24.5 g/dL. Her blood film shows hypochromia, microcytosis, and poikilocytosis including elliptocytes (pencil cells), target cells, and acanthocytes. Some Howell-Jolly bodies are present. Which of the following is the most likely diagnosis?

- A. β -Thalassemia heterozygosity
- B. Chronic blood loss
- C. Celiac disease
- D. Congenital sideroblastic anemia
- E. Dietary iron deficiency

Answer: C The blood count is suggestive of iron deficiency, not β -thalassemia heterozygosity (in which moderately severe anemia would not be expected). The blood film shows the features of iron deficiency (hypochromia, microcytosis, and pencil cells) and of hyposplenism (acanthocytes, target cells, and Howell-Jolly bodies). The combination of hyposplenism and iron deficiency suggests a diagnosis of celiac disease with splenic atrophy (Chapter 159). (Croese J, Harris O, Bain BJ. Coeliac disease. Haematological features and delay in diagnosis. *Med J Aust*. 1979;ii:335-338.)

5. A 24-year-old woman who was hypertensive during pregnancy has an epileptiform convulsion 24 hours postpartum. She has jaundice, edema, and proteinuria. An urgent blood count shows leukocytosis, neutrophilia, anemia, and thrombocytopenia. Her blood film confirms the thrombocytopenia and in addition shows left shift, toxic granulation, and red cell fragments (schistocytes). Which of the following is the most appropriate diagnosis?

- A. Disseminated intravascular coagulation
- B. Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome
- C. Hemolytic-uremic syndrome
- D. Preeclampsia
- E. Thrombotic thrombocytopenic purpura

Answer: B This syndrome is a severe form of preeclampsia/eclampsia, occurring during pregnancy or within 48 hours of delivery. The hemolytic anemia is microangiopathic in nature, and the detection of schistocytes is diagnostically useful. (Bain BJ, Riches J. Help with HELLP. *Am J Hematol*. 2010;85:70; Zini G, d'Onofrio G, Briggs C, et al; International Council for Standardization in Haematology [ICSH]. ICSH recommendations for identification, diagnostic value, and quantitation of schistocytes. *Int J Lab Hematol*. 2012;34:107-116.)

1. Which of the following laboratory tests would be *least* informative for establishing the presence of ineffective erythropoiesis in a patient with anemia?

- A. Serum lactate dehydrogenase (LDH)
- B. Serum bilirubin
- C. Reticulocyte count
- D. Serum erythropoietin level
- E. Bone marrow examination

Answer: D In patients with ineffective erythropoiesis, there is erythroid hyperplasia in the bone marrow. Therefore, the bone marrow examination (answer E) is informative. Moreover, these patients have markedly enhanced destruction of these erythroid precursors and, as a direct consequence, elevations of serum (nonconjugated) bilirubin (answer B) and LDH (answer A). Unlike patients with hemolytic anemia, the reticulocyte count (answer C) is low in ineffective erythropoiesis. In contrast to these informative tests, serum erythropoietin (answer D) is not helpful because it will be elevated in nearly all patients with anemia irrespective of pathogenesis.

2. What physiologic mechanism determines the regulation of erythropoietin levels in the plasma?

- A. Sensing of arterial oxygen tension in the carotid body
- B. Sensing of intracellular oxygen tension in the carotid body
- C. Sensing of arterial oxygen tension in the kidney
- D. Sensing of intracellular oxygen tension in the kidney
- E. Sensing of blood viscosity in the kidney

Answer: C The kidney is the primary site of erythropoietin production in humans and other mammals. The transcriptional regulation of the erythropoietin gene depends on the sensing of oxygen tension within a subset of renal interstitial cells at the boundary of the cortex and medulla. Note that sensing of arterial oxygen tension in the kidney (answer D) would not benefit the patient with anemia because arterial Po₂ would likely be normal. The sensing of oxygen tension in the carotid body (answers A and B) regulates the rate of respiration. Regulation of the red cell mass by sensing blood viscosity would be maladaptive (answer E).

3. Which of the following causes of anemia is best explained by inadequate production of erythropoietin?

- A. Uremia
- B. Chronic liver disease
- C. Iron deficiency
- D. Renal cell carcinoma
- E. Aplastic anemia

Answer: A In most patients with chronic renal failure (answer A), there is damage to cells at the medullary-cortical boundary that produce erythropoietin. Therefore, serum erythropoietin levels in these patients are inappropriately low. The liver (answer B) produces much less erythropoietin than the kidney, and therefore liver disease does not significantly affect erythropoietin production. Renal cell carcinoma (answer D) sometimes causes elevated levels of serum erythropoietin but never decreased levels. Serum erythropoietin is markedly elevated in patients with aplastic anemia.

4. Which of the following best characterizes the impact of hepcidin on iron homeostasis?

- A. Decreased release of iron from the duodenal enterocyte and decreased release of iron from the macrophage
- B. Increased release of iron from the duodenal enterocyte and decreased release of iron from the macrophage
- C. Decreased release of iron from the duodenal enterocyte and increased uptake of iron into the bone marrow
- D. Increased release of iron from the duodenal enterocyte and decreased uptake of iron into the bone marrow
- E. Increased release of iron from the duodenal enterocyte and increased uptake of iron into the bone marrow

Answer: A Hepcidin binds to and inactivates ferroportin, the transmembrane protein responsible for the export of iron from mucosal epithelial cells in the duodenum as well as macrophages in the bone marrow and liver. As a result, there is impairment of iron absorption from the gut and release of iron from macrophages.

5. What is the most effective way a patient compensates for anemia due to impaired red cell production?

- A. Increased heart rate and stroke volume
- B. Increased red cell oxygen affinity
- C. Decreased red cell oxygen affinity
- D. Decreased peripheral vascular resistance
- E. Increased production of erythropoietin

Answer: C By far the most effective way in which the anemic patient compensates for a reduction in red cell mass and oxygen carrying capacity is by elevation of red cell 2,3-DPG, which shifts the oxygen binding curve to the right and lowers oxygen affinity, thereby enhancing oxygen unloading to tissues. Erythropoietin production (answer E) is markedly enhanced in nearly all patients with moderate or severe anemia (except those with chronic renal failure), but the high levels of plasma erythropoietin are ineffective in boosting hemoglobin levels in those with impairment of red cell production. Increased resting heart rate and stroke volume (answer A) occur only in patients with severe anemia, and neither these cardiac changes nor decreased peripheral vascular resistance (answer D) are efficient modes of compensation.

1. A 60-year-old woman with a history of chronic arthritis that is currently under good control presents with symptoms of increased fatigue. She is noted to have a decreased hemoglobin of 8 g/dL and microcytic indices on her complete blood count. There is no evidence of blood loss by history or laboratory testing. The patient has a normal erythrocyte sedimentation rate (ESR) and a normal C-reactive protein (CRP) level. Which of the following routine laboratory tests is most likely to indicate whether this patient will respond to oral iron replacement with improvement in her hemoglobin level?

- A. Transferrin saturation level
- B. Serum ferritin level
- C. Serum iron level
- D. Vitamin B12 level
- E. Reticulocyte count

Answer: B The ferritin level is generally the best clinically available indicator of available iron for erythropoiesis. Although inflammation associated with arthritis could falsely elevate the estimation of iron stores associated with ferritin, this patient's arthritis is not highly active, as shown by the normal ESR and CRP level. Elevated CRP and ESR are indicative of even subclinical inflammation. Because these are normal, a ferritin level in this individual would likely indicate whether there is iron deficiency. Moreover, there are criteria for correcting ferritin levels in the presence of low or moderate inflammation.

The use of soluble transferrin receptor (sTfR) assay and sTfR/ferritin ratio may provide a more accurate test for iron deficiency than ferritin level in the setting of inflammatory disease. However, this test is not routinely available, and a recent meta-analysis suggests that further data are needed to define its overall diagnostic usefulness. (See Diagnosis under Iron Deficiency Anemia.) (Thurnham DI, McCabe LD, Halder S, et al. Adjusting plasma ferritin concentrations to remove the effects of subclinical inflammation in the assessment of iron deficiency: a meta-analysis. *Am J Clin Nutr.* 2010;92:546-555; Infusino I, Braga F, Dolci A, et al. Soluble transferrin receptor (sTfR) and sTfR/log ferritin index for the diagnosis of iron-deficiency anemia: a meta-analysis. *Am J Clin Pathol.* 2012;138:642-649.)

2. A 55-year-old man with metastatic colon cancer presents 6 months after completing chemotherapy with complaints of fatigue. His complete blood count shows a hemoglobin level of 10 g/dL with microcytic, normochromic indices, and his serum ferritin level is in the high-normal range. He has no history or physical findings of cardiovascular disease. He requests some kind of treatment for his anemia. Which of the following is the most appropriate recommendation?

- A. Erythropoietin injections to increase his hemoglobin level
- B. Begin red cell transfusions to maintain a hemoglobin of 12g/dL or higher
- C. Advise that his fatigue may be somewhat affected by his hemoglobin level but that treatment to increase his hemoglobin level alone is unlikely to improve his symptoms and carries significant risks
- D. Oral folate replacement
- E. Oral pyridoxine therapy

Answer: C Although erythropoietin injections have been documented to improve quality of life and performance status in patients with cancer and a hemoglobin of less than 10 g/dL who are undergoing chemotherapy, strong data supporting this therapy in patients with a hemoglobin of 10 g/dL or higher is lacking. The same is true for red cell transfusions, in the absence of symptomatic cardiovascular disease. In cancer patients not on chemotherapy, large meta-analyses of randomized trials have shown increased mortality and cancer progression in those treated with erythropoietin for anemia. In the absence of documented folate deficiency or sideroblastic anemia, there is no clear evidence that either folic acid replacement or pyridoxine therapy is of benefit in this setting. (See Treatment under Anemia of Chronic Disease and Inflammation.) (Ludwig H, Crawford J, Osterborg A, et al. Pooled analysis of individual patient-level data from all randomized, double-blind, placebo-controlled trials of darbepoetin alfa in the treatment of patients with chemotherapy-induced anemia. *J Clin Oncol.*

2009;27:2838-2847; Bohlius J, Schmidlin K, Brillant C, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. *Lancet*. 2009;373:1532-1542.)

3. An otherwise healthy 20-year-old woman with a history of excessive menstrual bleeding and increased fatigue was found to have a hemoglobin of 7 g/dL with microcytic, hypochromic indices, a low ferritin level, a low serum iron level, and reticulocyte count of 1.2%. Her menstrual bleeding pattern was normalized by hormone therapy, and she was begun on oral iron replacement with ferrous sulfate 350 mg three times daily. After 2 months, her hemoglobin was 8 g/dL, and there was no change in her other hematologic test results. After a full course of 2 g of intravenous iron gluconate, her hemoglobin, red cell indices, and iron level were partially corrected, but she remained somewhat anemic with a hemoglobin of 10 g/dL. A C-reactive protein (CRP) level and an ??1-acid glycoprotein (ACP) level were both normal. Which of the following laboratory tests would be most helpful to potentially explain her lack of complete response to iron therapy?

- A. Reticulocyte count
- B. Serum vitamin B12 level
- C. Bone marrow biopsy
- D. Genetic analysis for mutation in the *TMPRSS6* gene
- E. RDW on automated complete blood count

Answer: D This patient presents with classic routine laboratory findings of iron deficiency anemia. The failure to respond to oral iron replacement therapy suggests some reason for refractoriness to iron absorption. The patient is otherwise healthy, with no findings suggestive of malabsorption or inflammation or other reason to have high hepcidin levels that could account for this. However, the fact that intravenous iron supplementation only partially corrects the patient's anemia and iron deficiency suggests the presence of an excessive hepcidin level. Because the CRP and ACP levels were normal, demonstrating no evidence of inflammation to account for an elevated hepcidin level, it could be caused by a mutation in the *TMPRSS6* gene, which encodes the matriptase-2 protein that acts to suppress excess hepcidin production. Mutations in *TMPRSS6* can be either sporadic or familial. (See Failure to Respond to Iron Therapy under Iron Deficiency Anemia.) (Guillem F, Lawson S, Kannengiesser C, et al. Two nonsense mutations in the *TMPRSS6* gene in a patient with microcytic anemia and iron deficiency. *Blood*. 2008;112:2089-2097; Finberg KE. Iron-refractory iron deficiency anemia. *Semin Hematol*. 2009;46:378-386.)

4. A healthy 25-year-old man who was in a minor auto crash was found to have a microcytic, hypochromic anemia (hemoglobin 10 g/dL), unrelated to the accident, because there was no blood loss. The remainder of the complete blood count was normal. The patient was noted to be mildly ataxic but had no alcohol or drugs detectable on screening, and there was no head trauma. Serum iron level was normal, and serum ferritin level was in the high normal range. Workup for evidence of tumor or subclinical inflammation was negative, as was any history of prior drug or toxin exposure. A bone marrow showed normal hematopoiesis but demonstrated ringed sideroblasts. Which of the following tests or procedures is most likely to be useful for determining the underlying cause of this patient's anemia?

- A. Upper gastrointestinal endoscopy
- B. Genetic testing for mutations of the *TMPRSS6* gene
- C. Serum transferrin receptor level assay
- D. Genetic testing for gene mutations of the genes coding for the adenosine triphosphate-binding cassette gene (*ABC-7*) and the *ALAS-2* gene
- E. Serum folate level assay

Answer: D This patient has a moderate anemia that is not symptomatic, so it could have existed for many years undetected. Despite hypochromic and microcytic red cell features, there is no evidence of occult blood loss, and specific laboratory tests for diagnosing iron deficiency and inflammatory con-

ditions were negative. The presence of ringed sideroblasts in an otherwise healthy young male with no history of drug or toxin exposure suggests that this may be a congenital X-linked sideroblastic anemia. The two major X-linked hereditary types of sideroblastic anemia result from mutations in either the erythroid-specific δ -aminolevulinic acid synthase gene, also known as *ALAS-2*, or the adenosine triphosphate-binding cassette gene (*ABC-7*). X-linked sideroblastic anemias are often mild with minimal or no symptoms and therefore may go undetected until a supervening process results in symptomatic anemia or they are detected incidentally, such as in this case. The presence of mild ataxia in this young male would be most consistent with a subgroup of patients with *ABC-7* gene mutations who have associated ataxia.

(See Genetics under Sideroblastic Anemias.) (Camaschella C. Hereditary sideroblastic anemias: pathophysiology, diagnosis and treatment. *Semin Hematol*. 2009;46:371-377; Harigae H, Furuyama K. Hereditary sideroblastic anemia: pathophysiology and gene mutations. *Int J Hematol*. 2010;92: 425-431.)

5. A 60-year old man with chronic renal failure who is on hemodialysis has a falling hemoglobin level despite having been on erythropoietin (epo) therapy for a documented low serum epo level. His peripheral blood smear shows microcytic hypochromic red blood cells, and serum iron levels are low, but the serum ferritin level is 120 $\mu\text{g/dL}$. A bone marrow biopsy shows absent sideroblasts, and workup for occult blood loss is negative. Which of the following therapeutic interventions is likely to be the safest and most effective for increasing the patient's hemoglobin level?

- A. Oral iron supplement with ferrous sulfate
- B. Intravenous iron gluconate injections
- C. Doubling the dose of erythropoietin
- D. Intravenous iron dextran injections
- E. Oral iron supplementation with ferrous fumarate.

Answer: B The clinical setting and laboratory findings in this patient are all consistent with coexistent anemia of chronic disease and iron deficiency. The normal ferritin level is most likely due to the chronic inflammation seen in patients with renal failure on hemodialysis. Increasing the dosage of erythropoietin in this setting in the absence of increasing available iron for erythropoiesis is unlikely to be beneficial and may introduce increased risk for thrombosis. Oral iron supplementation is usually ineffective in the setting of chronic inflammation due to elevated hepcidin levels that block iron uptake by the gastrointestinal mucosa. Intravenous iron therapy has been demonstrated to be effective in increasing the response to erythropoietin in patients with chronic renal failure. Although both iron dextran and iron gluconate are effective in this setting, iron gluconate has been shown to be safer. (See Parenteral Administration under Iron Deficiency Anemia.) (Michael B, Coyne DW, Fishbane S, et al; Ferrlecit Publication Committee. Sodium ferric gluconate complex in hemodialysis patients: adverse reactions compared to placebo and iron dextran. *Kidney Int*. 2002;61:1830-1839; Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. *Blood*. 2010;116:4754-4761; Albaramki J, Hodson EM, Craig JC, et al. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. *Cochrane Database Syst Rev*. 2012;1:CD007857.)

1. A 68-year-old man is admitted to the intensive care unit because of acute respiratory failure secondary to clinically diagnosed community-acquired pneumonia. His temperature on admission is 41.2° C. Chest radiograph shows diffuse bilateral infiltrates. He is intubated and placed on a respirator, cultured, promptly started on broad-spectrum antibiotics, and placed on a cooling blanket. Intravenous hydration is begun. On the second day, the patient's condition deteriorates. Acrocyanosis develops in his fingertips and toes, the sclerae are noted to be icteric, and the urine from his Foley catheter has turned red (testing 4+ positive for heme but with only a small number of red blood cells). The admission hemoglobin of 14.2 has dropped to 7.8. What is the most likely cause of the acute anemia?

- A. Gross hematuria possibly secondary to ureteral trauma or a previously undiagnosed genitourinary malignancy
- B. Fulminant alveolar hemorrhage
- C. Warm antibody-mediated autoimmune hemolytic anemia most likely secondary to previously undiagnosed, widely metastatic lung cancer
- D. Drug-induced autoimmune hemolytic anemia, possibly caused by one of the antibiotics started on admission, with intravascular hemolysis
- E. Acute cold antibody-mediated autoimmune hemolytic anemia and agglutination secondary to *Mycoplasma pneumoniae* infection

Answer: E Although unusual, community-acquired *M. pneumoniae* infection can present with bilateral pulmonary infiltrates and acute respiratory failure. *M. pneumoniae* infection (as well as certain viral infections) are associated with cold-reactive autoantibody-mediated cold agglutinin and simultaneously hemolytic disease. This patient's abrupt onset of massive intravascular hemolysis could have been triggered by artificially cooling his body temperature. The patient's intravascular cold autoimmune hemolytic anemia (AIHA) is manifested by hemoglobinuria and his acute intravascular cold agglutinin disease by the development of acrocyanosis. The patient does not have gross hematuria; he has gross hemoglobinuria, so genitourinary tract disease cannot be the cause. Fulminant alveolar hemorrhage could cause a precipitous decline in hemoglobin but is very unlikely in the absence of bloody airway secretions via his endotracheal tube. Warm antibody-mediated AIHA secondary to cancer would not be expected to begin suddenly on hospitalization and would not explain the acrocyanosis. It would be too early for drug-induced hemolysis to begin in this way on the second day of admission.

2. Which of the following statements about chronic cold agglutinin disease is incorrect?

- A. It occurs mainly in young women, sometimes with other autoimmune disorders.
- B. It is mediated by IgM autoantibody.
- C. The direct antiglobulin (Coombs) test result is positive for only complement on the red blood cell surface.
- D. It is associated with neoplastic B-cell lymphoproliferative disorders in most cases.
- E. Splenectomy not effective in its treatment.

Answer: A Chronic cold agglutinin disease occurs in the great majority of cases in adults older than the age of 50 years. It is generally mediated by a complement-fixing monoclonal IgM autoantibody directed at the red blood cell (RBC) I antigen. However, when a direct antiglobulin test (DAT) is performed, the result is typically positive only for complement that remains fixed to the RBC membrane, and the associated IgM is readily eluted at room temperature before it can be detected in vitro. The great majority of patients with chronic cold agglutinin disease are now recognized to have an underlying B-cell lymphoproliferative neoplasm, such as non-Hodgkin lymphoma or chronic lymphocytic leukemia. The liver, not the spleen, is the major site of extravascular hemolysis in this disease, so splenectomy is not effective treatment.

3. A 45-year-old woman who has been treated in the past for presently clinically inactive systemic lupus erythematosus (SLE) presents with a recent onset of fatigue, lightheadedness, and yellowness of her eyes. Her hemoglobin is found to be 6.3 g/dL (with a baseline of about 12.5-13.0), reticulocytes are 15%, indirect bilirubin is 2.8 IU/L, and LDH is 840 mg/dL. A peripheral blood smear shows a large number of polychromatic red cells and spherocytes. Her direct antiglobulin test (Coombs test) result is positive for IgG. Her treatment at this time should include

- A. plasmapheresis.
- B. rituximab plus danazol.
- C. intravenous methylprednisolone.
- D. urgent splenectomy.
- E. restarting her previous SLE treatment with azathioprine.

Answer: C This patient has severe warm antibody-mediated autoimmune hemolytic anemia (AIHA), which is probably related to her history of SLE. It appears to be sufficiently acute and severe to require transfusions of packed red blood cells, although the blood bank will likely have difficulty with typing and crossmatching. (The latter problem should not deter giving transfusions in a case like this in consultation with the transfusion medicine specialist on call, often having to resort to transfusing with not completely matched but the “best-matched” units of blood available.) High-dose corticosteroids are the mainstay of initial therapy. Rituximab, danazol, and splenectomy are all second-line treatment options. Plasmapheresis is usually ineffective because at least 50% of an individual’s IgG (in this case, IgG autoantibody) is distributed into the extravascular space at any given time. Although azathioprine may have been effective in controlling this patient’s other manifestations of SLE in the past, it is not good initial therapy for AIHA.

1. A man recently diagnosed with glucose-6-phosphate dehydrogenase (G6PD) deficiency after an episode of hemolysis after taking chloroquine malaria prophylaxis before visiting Benin. He has many questions, including about starting a family. At the end of the visit, you provide several suggestions. These include all of the following except

- A. always inform health care providers that he is G6PD deficient, particularly before they prescribe any medication.
- B. seek medical attention if he is feeling tired, short of breath, and experiencing palpitations and if dark-colored urine is observed.
- C. he should avoid eating fava beans and fava plant-derived food.
- D. if his wife does not have G6PD deficiency, all sons will be unaffected, and all daughters will be carriers.
- E. if his wife is a G6PD carrier, one of two daughters will be G6PD deficient, one out of two daughters will be G6PD carriers, and his sons will not be affected.

Answer: E Glucose-6-phosphate dehydrogenase (G6PD) deficiency is inherited in an X-linked manner. Thus, if his wife does not have G6PD deficiency, all sons will be unaffected, and all daughters will be carriers (answer D). However, if his wife is a G6PD carrier, one of two daughters will be G6PD deficient, one of two daughters will be G6PD carriers, one son of two will be G6PD deficient, and one son of two will be unaffected. With the diagnosis of G6PD deficiency, he should always tell his health care providers, especially when they are prescribing medications, and he should avoid fava beans and all fava-derived products. Finally, he should seek medical attention when experiencing the symptoms of a hemolytic reaction, tiredness, shortness of breath, palpitations, and dark-colored urine.

2. You have just diagnosed a 23-year-old patient with hereditary spherocytosis. Which of the following are appropriate actions?

- A. Obtain ultrasonography of the spleen and gallbladder.
- B. Counsel the patient to avoid oxidant-inducing foods and medications.
- C. Determine if other family members could be affected and should be evaluated for the presence of hereditary spherocytosis.
- D. Counsel regarding possible occurrence of hemolytic and aplastic crises.
- E. A, B, and C
- F. A, C, and D
- G. All of the above

Answer: F Assessing spleen size and the biliary tract for the presence of cholelithiasis (answer A), determining if other family members could be affected after diagnosing a patient with hereditary spherocytosis (answer C), and counseling regarding hemolytic and aplastic crises (answer D) are all appropriate actions after diagnosing a patient with hereditary spherocytosis. Avoidance of oxidant-inducing food and medications (answer B), which is appropriate in patients with metabolic disease of the erythrocyte, especially glucose-6-phosphate dehydrogenase deficiency, is not necessary in hereditary spherocytosis.

3. You are asked to see a jaundiced 62-year-old man with cirrhotic liver disease complicated by portal hypertension and hepatosplenomegaly because of stomatocytes on peripheral smear. He is being evaluated for splenectomy. His total leukocyte count is 4000/mm³ and his platelet count is 105,000/m³. Hemoglobin and hematocrit are 8.4 g/dL and 26%, respectively. Peripheral blood smear shows decreased numbers of leukocytes and platelets. Erythrocyte morphology reveals nearly 100% stomatocytes, erythrocytes with a central bar, and a few target cells. Your most appropriate response would be

- A. the presence of stomatocytes makes splenectomy an absolute contraindication.
- B. obtain erythrocyte electrolyte determinations.
- C. prominent stomatocytosis is common in patients with severe liver disease and no additional specific therapy is indicated.
- D. obtain cholesterol and triglyceride levels to correlate with severity of stomatocytes and target cells and consider lipid lowering therapy.
- E. obtain osmotic fragility or EMA binding test.

Answer: C Prominent stomatocytosis is common in patients with severe liver disease, and no additional specific therapy is indicated. Marked stomatocytosis is very common in advanced liver disease. Target cells may also be seen in advanced liver disease. Splenectomy is contraindicated in cases of hereditary stomatocytosis, not in cases of acquired stomatocytosis (answer A). Evaluation for hereditary stomatocytosis or hereditary spherocytosis via erythrocyte electrolytes (answer B), osmotic fragility or EMA binding (answer E) without additional historical data is not necessary. Although erythrocyte membrane lipids and cholesterol are perturbed in stomatocytosis, specific therapy is not warranted.

4. A 31-year old woman presents with a history of lifelong hemolytic anemia. Her parents are normal, but a sister also has anemia. She tells you she had a splenectomy as a teenager, but "it didn't work." Laboratory evaluation reveals hemoglobin of 10 g/dL, hematocrit of 31%, mean corpuscular volume of 96 fL, and reticulocyte count of 15%. The lactate dehydrogenase level is 750 IU/L. Peripheral blood smear shows evidence of hemolysis; many erythrocytes show prominent basophilic stippling. Her likely diagnosis is

- A. pyruvate kinase deficiency.
- B. glucose-6-phosphate dehydrogenase deficiency.
- C. hereditary spherocytosis.
- D. hereditary stomatocytosis.
- E. pyrimidine 5'-nucleotidase deficiency.

Answer: E All of the disorders listed may be associated with a history of lifelong anemia. Pyruvate kinase and pyrimidine 5'-nucleotidase (P5N) deficiency are both recessively inherited (normal parents, affected sister.) Splenectomy failure is typical in P5N deficiency and some cases of hereditary stomatocytosis, in which splenectomy is contraindicated. Basophilic stippling of erythrocytes is a characteristic finding in P5N deficiency because of the accumulation of partially degraded, nondiffusible RNAs in the cell.

5. Evaluation of a patient with hemolytic anemia reveals the presence of spherocytes on peripheral blood smear. Which disorder is NOT in the differential diagnosis?

- A. Heinz body hemolytic anemia
- B. Autoimmune hemolytic anemia
- C. Hereditary stomatocytosis
- D. Hereditary spherocytosis
- E. Liver disease

Answer: C Although the results of osmotic fragility testing may be similar in patients with hereditary stomatocytosis and hereditary spherocytosis, spherocytes are rarely seen on the peripheral blood smear in those with hereditary stomatocytosis. In addition to hereditary spherocytosis, spherocytes may be seen on the peripheral blood smear of patients with Heinz body hemolytic anemia, autoimmune hemolytic anemia, and liver disease.

Ch / 162 THE THALASSEMIAS

1. An 18-year-old woman from Pakistan has been observed for a lifelong severe, microcytic and hypochromic anemia. Her hemoglobin levels have generally been in the range of 7 to 10 g/dL, but she recalls needing blood transfusions only twice in her life, on both occasions after traumatic bone fractures. Throughout childhood, her parents had kept her from playing sports or participating in activities requiring significant physical exertion because they had been told by pediatricians that she had a "weak heart." She had markedly delayed puberty but now had regular menses. Physical examination shows marked hepatosplenomegaly; laboratory test abnormalities include indirect hyperbilirubinemia and hyperglycemia. What is the most likely diagnosis?

- A. β -Thalassemia major
- B. Homozygosity for hemoglobin E (HbEE)
- C. Hemoglobin H (HbH) disease
- D. Hydrops fetalis
- E. Hereditary juvenile hemochromatosis

Answer: C The clinical picture is most consistent with thalassemia intermedia. In the case of α -thalassemia, this would be most like hemoglobin H disease (most frequently resulting from the interaction of α^{+} - and α^0 -thalassemia), with the β_4 tetramers of hemoglobin H forming red cell inclusion bodies leading to chronic hemolysis. Patients with α - or β -thalassemia intermedia become severely iron overloaded from lifelong hyperabsorption of dietary iron, even without needing blood transfusions. A similar gut hyperabsorption of iron occurs in familial hemochromatosis states, but those individuals are not typically anemic. This patient's hyperglycemia, growth retardation, possibly her bone fragility, and even the history of a "weak heart" (perhaps due to cardiomyopathy) are all manifestations of systemic iron overload. Thalassemias are especially prevalent not only in people of Mediterranean and Middle Eastern origin but also in those from the Indian subcontinent. In contrast to thalassemia intermedia, a patient with β -thalassemia major would be expected to be transfusion dependent throughout life. Hydrops fetalis, in which all four α -globin genes are deleted, is incompatible with life. Hemoglobin E, even in its homozygous state, causes little if any anemia and microcytosis.

2. Which of the following statements is correct regarding hematopoietic stem cell transplantation for thalassemia?

- A. It can lead to thalassemia-free survival of at least 85% in low-risk, younger patients.
- B. It should not be administered with cord blood for transplantation.
- C. It has been mostly effective in the α -thalassemias.
- D. It is mostly reserved for thalassemia patients who are poorly iron chelated and have liver involvement.
- E. It is associated with a reduced risk of graft-versus-host disease compared with comparable unrelated transplants for other hematologic diseases.

Answer: A The highest risk indicators in hematopoietic stem cell transplantation for thalassemia are hepatomegaly, hepatic fibrosis, and poor iron chelation history. On the other hand, the Pesaro group's experience has demonstrated 87% disease-free survival in thalassemia patients who are younger than 17 years at the time of transplantation, have none of the risk factors noted, and are allografted from an HLA-identical related donor. Early experience with cord blood transplantation has shown it to be a safe procedure for thalassemia patients. Hematopoietic stem cell transplantation has been mainly successful in β -thalassemia. The risk of graft-versus-host disease (acute and chronic) after bone marrow transplantation from unrelated donors is at least as high in thalassemia as it is in other indications for bone marrow transplantation.

3. Heterozygosity for hemoglobin E

- A. Is a rare form of unstable hemoglobinopathy
- B. Is associated with lifelong, low-grade hemolysis
- C. Causes iron overload from hyperabsorption of dietary iron
- D. Is frequently associated with iron deficiency
- E. Is of little if any clinical significance

Answer: E Hemoglobin E is one of the most common mutations in the world, especially in the Indian subcontinent and Southeast Asia. Its phenotype is that of a mild thalassemia, not an unstable hemoglobinopathy. It is of little if any clinical importance in its heterozygous form (HbE trait); even individuals who are homozygous for hemoglobin E (HbEE) usually have only mild anemia and microcytosis, without any clinical sequelae. Hemoglobin E can be mistaken for iron deficiency in the absence of further laboratory testing, but it is not known to be associated with iron deficiency.

1. A 40-year-old man with sickle cell anemia (HbSS) requires open lung resection of a newly diagnosed and localized non-small cell lung cancer. He has had numerous hospitalizations in the past for sickle crises, including acute chest syndrome, and was taking hydroxyurea until about 3 years ago, when he discontinued it and was lost to follow-up. His complete blood count now is as follows: white blood cells, 11,000; hemoglobin, 9.5; hematocrit, 25.5; platelets, 420,000; reticulocytes, 4.5%. These values are similar to those he has had in the past. What preoperative management related to his sickle cell anemia should be recommended?

- A. Transfusion of red blood cells to a hematocrit of about 30%
- B. Exchange transfusions and initiation of iron chelation therapy
- C. Hydroxyurea with a loading dose and then his previous maintenance dose
- D. Erythropoietin therapy
- E. None of the above but close hemodynamic and hematologic monitoring

Answer: A Cautious preoperative blood transfusion can improve surgical outcomes. Simple preoperative red cell transfusions to a hematocrit of about 30% are as effective as exchange transfusions to prevent postoperative complications, and they cause fewer transfusion-related complications. See the section Surgery and Anesthesia and reference A7 to the Transfusion Alternatives Preoperatively in Sickle Cell Disease ((TAPS) study, a randomized, controlled, multicenter clinical trial. Chronic iron chelation therapy is effective in the treatment of transfusional iron overload, but it is not urgent to begin it preoperatively, especially because he has not even had baseline magnetic resonance imaging evaluation for his level of iron overload (see the section Red Blood Cell Transfusion and Iron Chelation Therapy). Judicious use of erythropoietin therapy may be considered in sickle cell disease patients with renal failure, but even in those individuals, its effects on increasing the hematocrit are gradual in onset and unpredictable.

2. A 25-year-old woman with sickle cell anemia (HbSS) is brought to the emergency department after an episode of syncope. She has been observed regularly in the comprehensive sickle cell center of the hospital and has been taking hydroxyurea 500 mg daily for the past 4 years, which has been associated with a marked decrease in painful sickle crises. Blood counts have been regularly monitored during the hydroxyurea therapy, and the most recent complete blood count 1 week ago showed the following: white blood cells, 7500; hemoglobin, 9.9; hematocrit, 28.5; mean corpuscular volume, 106; platelets, 320,000; reticulocytes, 6.5%. On examination in the emergency department, she is sluggishly responsive, is hypotensive, and has a thread pulse with a rate of 140. There is mild, diffuse abdominal tenderness but no organomegaly or mass palpable. Stat complete blood count now shows the following: white blood cells, 8500; hemoglobin, 3.8; hematocrit, 17.2; reticulocytes, 0.2%; platelets, 410,000. What is the most likely diagnosis?

- A. Acute vaso-occlusive crisis
- B. Sequestration crisis
- C. Marrow suppression by hydroxyurea
- D. Aplastic crisis
- E. Hyperhemolytic crisis

Answer D Acute anemia in patients with HbSS can have several causes, as described in the section Acute Anemia. A simple vaso-occlusive crisis should not be accompanied by an acute drop in hemoglobin and hematocrit. Sequestration crisis occurs in young children (peak age, 2 years) who still have a functioning spleen; they present with massive and painful enlargement of the spleen, not seen in this case, due to trapping of sickle cells in splenic sinusoids. Myelosuppression by hydroxyurea is always a concern, but her blood counts have been closely monitored and were unchanged just a week ago; and even if she happened to take an inadvertently high dose of the drug in the interval, her severe anemia should have been accompanied by major decreases in the white blood cell and platelet counts as well. Hemolytic crisis is essentially ruled out by the very low reticulocyte count. Aplastic crisis in HbSS patients is a rare but life-threatening emergency that is characterized by pure red cell

aplasia typically as a result of parvovirus B19 infection. Parvovirus B19 has characteristic tropism for erythroid precursors and therefore causes severe erythroblastopenia in the bone marrow. Coupled with the ongoing brisk hemolysis of sickle cell disease, an abrupt shutdown of red cell production by the marrow leads to a precipitous fall in hemoglobin and hematocrit. In addition to aggressive but cautious red cell transfusions (to avoid fluid overload), intravenous immune globulin has been found to be effective by providing a large bolus of neutralizing antibodies to accelerate clearance of parvovirus B19.

Ch / 164 **MEGALOBLASTIC ANEMIAS**

1. A 42-year-old Asian woman presents with an 8-month history of progressive lethargy and fatigue, anhedonia, forgetfulness, menorrhagia, abdominal bloating and occasional diarrhea, paresthesias, and staggering in the dark. Physical examination reveals anemia with lateral tongue ulcers, mild vitiligo, thyromegaly, delayed ankle reflexes, and reduced vibration sense and proprioception. The hemoglobin level is 5 g/dL, the white blood cell count is 3000/mm³, and the platelet count is 130,000/mm³. The peripheral smear reveals a dimorphic picture with macro-ovalocytes and hypochromic microcytic red cells with marked anisocytosis and occasional teardrop cells. Several five-lobed and one six-lobed polymorphonuclear neutrophils are noted. Serum ferritin level is 5 ng/mL, serum cobalamin level is 800 pg/mL, and serum folate level is 5 ng/mL (lower limit of normal, <2.4 ng/mL). The thyroid-stimulating hormone concentration is 15 mIU/L. Which of the following is an *incorrect* statement?
 - A. Vegetarianism, pernicious anemia with or without hypothyroidism, celiac disease, and pregnancy in women not taking supplemental iron or folate can give a similar picture of dimorphic red cells on a peripheral blood smear.
 - B. Even without the Schilling test, it is possible to make the diagnosis of pernicious anemia with a noninvasive blood test.
 - C. Antiparietal cell antibodies, which are diagnostic for pernicious anemia, can interfere with the current serum tests for cobalamin deficiency.
 - D. The possibility of folate deficiency cannot be ruled out, given the current serum folate level.
 - E. Treatment with a combination of iron and ascorbic acid plus l-thyroxine alone will not resolve this patient's anemia because it is likely she has an added dietary deficiency of cobalamin.

Answer: C Anti-intrinsic factor antibodies can interfere with the cobalamin-binding luminescence assays and lead to a failure in diagnosis of pernicious anemia in those with classic symptoms and sign (as in this patient). By contrast, antiparietal cell antibodies have no influence on this test. The identification of serum anti-intrinsic factor antibodies is highly specific and diagnostic for pernicious anemia; by contrast, antiparietal antibodies are only about 50% specific for pernicious anemia. The presence of cobalamin deficiency can falsely raise the serum folate level, which could drop below normal on replenishment of cobalamin. This patient probably has a cobalamin deficiency due to either vegetarianism (and even near-vegetarianism) or a combination of pernicious anemia with hypothyroidism and vitiligo (commonly associated autoimmune diseases); in addition to iron, replacement of cobalamin will be needed for a full hematologic response. A dimorphic picture due to iron deficiency and either folate or cobalamin deficiency is found in all the conditions listed in A.

2. An 18-year-old unemployed white woman is to be prescribed generic phenytoin for epilepsy. She is asymptomatic except for passing clots during her periods and “memory problems,” and she has a hemoglobin level of 11 g/dL. She used to eat a balanced diet but has been on a vegetarian “low-carb diet” for the past 2 years ever since she learned two things from her favorite Hollywood actress: (1) her idol watches her weight by consuming small servings of salads and other organic-natural foods, and (2) she recently spoke out on a daytime television show about “our wanton exploitation of animals as a food source.” The patient has lost 10 pounds in the past 8 months. She has had occasionally irregular periods and is concerned about pregnancy because her boyfriend does not like condoms. Which of the following statements is *not* true?

- A. This patient’s anemia is likely to be due to a combined deficiency of iron, cobalamin, and folate.
- B. This patient is at risk for having a baby with neural tube defects because her diet is likely to be low in folate, and phenytoin can induce a folate deficiency.
- C. Taking folate before and during administration of phenytoin will reduce the possibility that she will develop gingival hyperplasia.
- D. The patient should be taking supplements of iron, cobalamin, and folate because her diet is likely to be low in these nutrients.
- E. At this time, the patient’s memory problems can be attributed to iron deficiency but not to either folate deficiency or cobalamin deficiency.

Answer: A Because she switched from a balanced diet to a vegetarian diet only 2 years ago, she is not at risk for dietary cobalamin deficiency; however, with prolonged vegetarianism for 5 years, she will need to be taking cobalamin supplements. Vegetarian diets are intrinsically low in bioavailable iron, but earlier she used to eat a balanced diet. Because carbohydrate (flour that makes bread and pasta) is the food source that is fortified with folic acid, her low-carb diet could be low in folate, even though she consumes “small servings of salads.” Because she does not take folate supplements, the impending initiation of phenytoin, which interferes with folate absorption, places her at risk for having a baby with a neural tube defect. Recent studies show that taking folate before and during administration of phenytoin will reduce the possibility that she will develop gingival hyperplasia. Although folate deficiency does not cause neuropsychiatric problems in adults, iron deficiency is notorious for cognitive problems in young women with minimal (iron deficiency–induced) anemia.

3. A 29-year-old Kenyan postgraduate year 2 medical resident at a major university hospital in the Midwest with known thalassemia minor is referred to you for advice. She was admitted a month ago with high fever and chills with drenching sweats. She had recently returned from a trip home, where she also got married. She mentioned that she had been bitten several times by mosquitoes during her honeymoon. Her dietary history is significant only for the fact that she cooks all her meals and subsists “mostly on *ugali* (organic cornmeal without additives) and kale or other sautéed vegetables, occasional (once per week) small servings of meat, and lots of tea.” In the hospital, a diagnosis of falciparum malaria was made on the basis of finding parasites on a peripheral smear. The accompanying laboratory results showed a hemoglobin level of 6 g/dL, mean corpuscular volume (MCV) of 90, and corrected reticulocyte count of 15%; lactate dehydrogenase was high, and haptoglobin was low. The serum folate level was well within the normal range (12 ng/mL; normal, >2 ng/mL), the cobalamin level was borderline low (202 pg/mL), and the serum ferritin level was high (300 ng/mL). Although antimalarials led to an eradication of malaria, the patient has still not significantly improved her hemoglobin level above 9 g/dL 2 months later. All of the following are true *except* which one?

- A. The patient is at risk for deficiencies of folate, cobalamin, and iron because her native Kenyan diet is monotonous and relatively low in both animal-source foods and fresh produce.
- B. The patient could have had a Coombs-positive as well as a Coombs-negative hemolytic anemia associated with falciparum malaria and should be prescribed both antimalarials and micronutrients to support compensatory hematopoiesis.
- C. At presentation in the hospital, the folate value rules out the possibility of folate deficiency and argues against administration of folic acid.

- D. If the patient is taking long-term folic acid in planning for a pregnancy, the development of neurologic symptoms should immediately trigger concerns of a cobalamin deficiency.
- E. She should now be treated with iron, cobalamin, and folate to effect a complete resolution of the anemia and then be maintained with these supplements to optimize her nutrition.

Answer: C Red cells normally contain 30-fold more folate than what is present in the serum. Therefore, hemolysis associated with malaria will release the 30-fold excess folate from red cells into the circulation and result in a falsely high serum folate value. Hence, the serum folate level is a poor test to use in this setting because it is falsely elevated in both malaria and cobalamin deficiency. In addition, the patient is likely to have a diet that is low in all three nutrients (folate, cobalamin, and iron); food frequency questionnaire–derived estimates from resource-limited countries (including Kenya) indicate that most women consume less than what is optimum. Near-vegetarian and vegetarian diets predispose to cobalamin and iron deficiency. The borderline nutritional cobalamin deficiency can also contribute to a falsely elevated folate level. Because the cornmeal she purchases has no additives (i.e., no folic acid), she will need to take folate supplements in preparation for pregnancy.

4. A 29-year-old white woman is referred because of easy fatigue and anorexia. During the past 5 years, she has noticed abdominal bloating and diarrhea that are closely linked to consumption of gluten-containing foods. There is pallor, and the hemoglobin level is 9 with an MCV of 90 and a serum ferritin level of 10 ng/mL. The serum anti–tissue transglutaminase antibody test result is positive. All of the following are true *except* which one?

- A. Treatment of the patient with total-dose parenteral iron will resolve the iron deficiency, but the anemia will likely persist.
- B. Treatment with iron alone will result in a progressive increase in MCV, which reflects unmasking of a megaloblastic anemia.
- C. The serum homocysteine and methylmalonic acid levels are likely to be increased and signify metabolic evidence of cobalamin deficiency.
- D. Folate deficiency is unlikely to be present in a patient with elevated methylmalonic acid and homocysteine from cobalamin deficiency.
- E. Folates are absorbed through the proton-coupled folate transporter in the jejunum, which can be involved in celiac disease.

Answer: D Because this patient has celiac disease, in the short term, folate deficiency can develop; but in the long term, with more extensive intestinal involvement that includes the ileum, cobalamin deficiency can eventually develop. The existence of high methylmalonic acid and homocysteine values, although confirming cobalamin deficiency, does not rule out an associated folate deficiency, which is associated with high homocysteine values. Despite low ferritin values consistent with iron deficiency from celiac disease, the normal MCV probably reflects an underlying folate or cobalamin deficiency. Treatment with parenteral iron will unmask the hematologic features of megaloblastic anemia.

5. A 58-year-old white man with type 2 diabetes for 15 years is evaluated for a 6- to 8-month history of slowly progressive fatigue, anemia, and mild peripheral neuropathy of both lower extremities. He had been well controlled with metformin 850 mg three times daily and only recently began taking a single dose of long-acting insulin at night because the latest hemoglobin A1c level was 10. He does not take supplements, and his diet has been well balanced. He regularly makes his own bread every 2 or 3 days. He has recently been prescribed proton pump inhibitors and an H2- blocker for dyspeptic symptoms. The hemoglobin level is 11 with an MCV of 108, with macro-ovalocytes and several five-lobed hypersegmented polymorphonuclear neutrophils seen on the peripheral blood smear. All of the following are true *except* which one?

- A. The patient has features of megaloblastic anemia and should have a bone marrow examination to confirm the diagnosis.
- B. The serum cobalamin level is likely to be low, but the serum folate level is likely to be in the high-normal range.
- C. This patient could have food cobalamin malabsorption because of inhibition of acid in the stomach.
- D. This patient could have cobalamin malabsorption at the level of cubam receptors in the ileum.
- E. Upper endoscopy is indicated to look for gastrinomas or gastric cancer if anti-intrinsic factor antibodies are found.

Answer: A In view of the slowly progressive nature of the anemia, the characteristic findings of a megaloblastic anemia on the peripheral smear, and the known effect of metformin in interfering with trans-enterocytic transport of cobalamin (at the ileal level), there is no reason to proceed with a bone marrow examination. The serum cobalamin level is likely to be low after consumption of metformin for 5 years (this patient has been taking metformin for much longer—15 years); the serum folate level is likely to be high-normal among those consuming a balanced diet because of food fortification with folic acid (remember, he makes his own bread). The malabsorption of cobalamin in the stomach induced by a reduction of acid can, during several years, lead to symptoms of deficiency. Proton pump inhibitors and H₂- blockers can induce malabsorption. However, the primary mechanism of metformin is believed to be at the level of cubam receptors in the ileum, where supplemental calcium (1.2 g/day) taken with the drug can prevent this well-recognized, potentially serious but reversible, delayed adverse effect of metformin.

1. A 20-year-old man with severe aplastic anemia is diagnosed by chromosomal breakage testing to have Fanconi anemia. Which of the following would be the preferred first-line treatment?
 - A. Antithymocyte globulin (ATG)
 - B. Bone marrow transplant from a matched related donor after fludarabine-based conditioning
 - C. Cord blood hematopoietic stem cell transplant after conditioning that includes irradiation
 - D. Supportive therapy with erythropoiesis-stimulating agents (ESAs) and granulocyte colony-stimulating factor (G-CSF)
 - E. Cyclosporine

Answer: B None of these is an entirely satisfactory first-line therapy for aplastic anemia caused by an inherited bone marrow failure syndrome (Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia), as in this case. These patients do not respond to ATG and other immunosuppressive therapies (including cyclosporine). Growth factors like ESAs and G-CSF are generally ineffective in severe aplastic anemia. Hematopoietic stem cell transplantation (HSCT) that includes irradiation in the conditioning regimen exposes the patient to an additional risk factor interacting with the main underlying biologic defect of Fanconi anemia, the DNA repair process. The use of specifically bone marrow as the source of HSCT and reduced-intensity conditioning regimens with fludarabine appear to have the most favorable outcome at this point, although it will not reduce the subsequent risk of a second malignant neoplasm. (Peffault de Latour R, Porcher R, Dalle JH, et al. Allogeneic hematopoietic stem cell transplantation in Fanconi anemia: the European Group for Blood and Marrow Transplantation experience. *Blood*. 2013;122:4279-4286).

2. Which of the following statements is not correct regarding inherited bone marrow failure syndromes?

- A. Most of the known genes inactivated in Fanconi anemia encode proteins that protect the genome from excessive damage induced by chemical cross-linking agents.
- B. Most of the known genes inactivated in dyskeratosis congenita encode proteins that participate in the maintenance of telomeres.
- C. Most of the known genes inactivated in Diamond-Blackfan anemia encode ribosomal proteins.
- D. The best screening test for Diamond-Blackfan anemia is the chromosomal breakage test.
- E. The best screening test for dyskeratosis congenita is quantitative analysis of telomere length (flow-FISH) in lymphocytes.

Answer: D Gene mutations for these three syndromes mostly involve inactivations of specific genes that encode the key proteins involved in their molecular pathogenesis, respectively, as correctly indicated in choices A to C. These also form the basis of screening tests for Fanconi anemia and dyskeratosis congenita; however, there are no adequate screening tests for Diamond-Blackfan anemia. (For Diamond-Blackfan anemia, serum adenosine deaminase is often elevated, but this does not represent a screening test.) Gene sequencing can provide specific mutation analysis for all three of these syndromes, when needed.

3. In a patient with pancytopenia, which of the following abnormalities in the peripheral blood smear would provide a useful indicator that the cause of the pancytopenia is aplastic anemia?

- A. Hypersegmented polymorphonuclear leukocytes
- B. Nucleated red cells
- C. Teardrop-shaped red cells
- D. Giant platelets
- E. None of the above

Answer: E The peripheral blood smear in aplastic anemia is generally normal, even in severe cases. This does not mean that the peripheral blood smear does not provide useful information about the etiology of pancytopenia in many cases. For example, hypersegmented polymorphonuclear leukocytes (A) suggest megaloblastic anemia (which in more advanced stages can cause pancytopenia, not just anemia). Nucleated (B) and teardrop-shaped (C) red cells suggest a “myelophthitic” process that involves invasion of the bone marrow by “foreign” elements (like metastatic cancer, fibrosis, or granulomas).

1. A 65-year-old man with coronary artery disease, hypertension, chronic obstructive pulmonary disease, and an active 40 pack year smoking history is referred by his primary care physician because of gradually increasing hemoglobin and hematocrit over the past 5 years. On physical examination, his spleen is not palpable. His blood counts now are hemoglobin, 18.9 g/dL; hematocrit, 60.5%; MCV = 78; white blood cell count, 11,200/ μ L (normal differential); and platelets, 485,000/ μ L. You are asked to evaluate the cause of this patient's polycythemia. Which of the following tests is most likely to either make or rule out the diagnosis of polycythemia vera in this case?

- A. Carboxyhemoglobin level
- B. Abdominal ultrasonography findings for spleen size
- C. PCR for *JAK2-V617F*
- D. Bone marrow aspirate and biopsy with cytogenetics
- E. Red blood cell mass

Answer: C Although it is not specific for polycythemia vera (PV), almost all patients with PV carry a *JAK2* mutation, and its absence makes the diagnosis questionable. (The *JAK2-V617F* mutation also occurs in about 60% of patients with essential thrombocythemia and 50% to 60% with primary myelofibrosis.) Differentiating PV from other secondary causes of polycythemia (see Table 166-5) can be challenging if the individual is negative for a *JAK2* mutation. Bone marrow aspirate and biopsy with cytogenetics can sometimes demonstrate characteristic findings of a myeloproliferative neoplasms, including trilineage hyperplasia (as opposed to just erythroid hyperplasia, the latter being what would be expected for the secondary polycythemias), as well as morphologic changes, but these are rarely absolutely diagnostic; furthermore, cytogenetic studies usually do not add to making or ruling out the diagnosis of PV. A red blood cell (RBC) mass determination is almost superfluous in this case because the great majority of patients with this degree of erythrocytosis, regardless of cause, will have elevated RBC masses. The finding of splenomegaly is neither specific nor sensitive for a diagnosis of PV, whether it is assessed by physical examination or by imaging. It would not be surprising to find an elevated level of carboxyhemoglobin in this smoker, but that would not be a conclusive finding for the diagnosis of his polycythemia. Not mentioned among the choices, a serum erythropoietin would be a helpful ancillary test in a case like this; in general, it would be expected to be elevated in virtually all of the polycythemias but low in PV (the latter because of feedback inhibition of erythropoietin by the kidneys as a result of the primary myeloproliferative process of PV).

2. Which of the following is *not* a known complication of polycythemia vera (PV) and essential thrombocythemia (ET)?

- A. Budd-Chiari syndrome
- B. Aplastic anemia
- C. Erythromelalgia
- D. Marrow fibrosis
- E. Acute leukemia

Answer: B Thrombosis is the major cause of morbidity and mortality in the myeloproliferative neoplasms, and it often presents in unusual intraabdominal sites such as hepatic vein thrombosis (Budd-Chiari syndrome) and portal and mesenteric vein thrombosis. Erythromelalgia is a striking and characteristic (but not specific) syndrome of microvascular vasomotor and occlusive disease, mostly affecting the dependent parts of the extremities, typically the feet and sometimes the hands. It is characterized by excruciating pain and tenderness in a patchy distribution, sometimes accompanied by corresponding patches of erythema and warmth. The large vessel peripheral pulses are usually intact. Erythromelalgia is generally very sensitive to prompt response to aspirin. Both marrow fibrosis and spontaneous transformation to acute leukemia are unusual but well-described feared complications of PV and ET. However, aplastic anemia is not associated with these diseases (in contrast to its association with a different bone marrow stem cell disease, paroxysmal nocturnal hemoglobinuria.)

3. Massive, painful splenomegaly develops in a 70-year-old woman with an established diagnosis of primary myelofibrosis (PMF). She is *JAK2-V617F* mutation negative but *CALR* mutation positive. She has become transfusion dependent and has been unresponsive to medical management of the splenomegaly. After much consideration of risks and benefits, it is decided to do a splenectomy. Which of the following are you most likely to find in the spleen on pathologic examination in this case?

- A. Megakaryocytes
- B. Fibrosis
- C. Hemophagocytosis
- D. Clonal lymphocytic infiltration
- E. Storage cells

Answer: A A major cause of this PMF patient's massive splenomegaly is likely to be extensive "extramedullary hematopoiesis" (EMH) within the spleen. EMH occurs in myeloid metaplasia with or without myelofibrosis. It represents essentially "ectopic" sites of renew hematopoiesis, recapitulating the normal fetal state where hematopoiesis was not restricted to bone marrow but also occurred in other organs such as the spleen and liver. Therefore, histopathology of this patient's spleen is likely to demonstrate many blood cell precursors, including megakaryocytes. Fibrosis, hemophagocytosis, and infiltration with storage cells are not characteristic findings in PMF (or any of the other myeloproliferative neoplasms [MPNs]). Clonal lymphocytic infiltration can cause splenomegaly in the lymphomas but not in the MPNs, which are clonal myeloproliferative, not lymphoproliferative, disorders.

4. A 72-year-old woman has been followed by her hematologist for more than 15 years with the diagnosis of polycythemia vera (PV) (recently confirmed by the finding of the *JAK2-V617F* mutation). Her only treatments during this time have been periodic phlebotomies as needed to maintain a hematocrit below 45%, varying doses of hydroxyurea, and one aspirin daily. Her blood counts have been well controlled, and she has been largely asymptomatic. Over the past several months, despite lowering the hydroxyurea dose from 2 g/day to 1 g/day to 500 mg/day and now to 500 mg on alternate days, the patient has been noted to be actually anemic. Her only new symptoms are increasing fatigue. Her hematocrits have been ranging from 35% to 40% over this time. She reports no signs or symptoms of bleeding, her stools are negative for occult blood, and her serum ferritin level is within normal limits. What would you do now?

- A. Carefully examine the peripheral blood smear.
- B. Do evaluation for occult malignancy, including imaging of chest, abdomen, and pelvis.
- C. Perform bone marrow aspirate and biopsy.
- D. Check *CALR* (calreticulin gene) mutation status to rule out clonal evolution of disease.
- E. Stop hydroxyurea completely and observe course of the anemia.

Answer: C The most likely diagnosis is that this patient's PV is now transforming to either myelofibrosis or acute leukemia (or myelodysplasia). This is the natural history of the disease in a small minority of patients with PV even in the absence of previous treatments with known leukemogenic agents (e.g., P32, alkylating agents). A peripheral blood smear is important and can provide important clues, including leukoerythroblastic or myelophthistic changes (e.g., teardrop-shaped red blood cells, nucleated red cells, and immature myeloid precursors) could indicate development of fibrosis; the presence of circulating blasts could indicate conversion to acute leukemia. However, whether or not one sees these changes on the blood smear, a bone marrow aspirate and biopsy are indicated as the definitive test. There is no clear evidence that patients with myeloproliferative neoplasms (MPNs) are predisposed to second solid tumor malignancies; therefore, other than conducting a thorough history and physical examination and then pursuing any leads found with further testing, general body imaging to look for occult malignancy is not indicated. Clonal evolution does occur in PV and the other MPNs, and new mutations can be acquired during the course of the disease. However, at this point, it appears that the *JAK2-V617F* and *CALR* mutations are mutually exclusive in the MPNs. Even if stopping the hydroxyurea slightly improves the anemia, the striking history of increasing sensitivity to hydroxyurea suggests that something unfavorable is happening in this patient's bone marrow.

1. A 20-year-old African American college student receives a scholarship to spend her junior year abroad in France. She needs to have a health form completed before her departure. A complete blood count (CBC) reveals neutropenia, and her physician advises her to postpone the scholarship and to see you for evaluation. She is healthy with no history of excessive infections. Her physical examination is normal. CBC shows: white blood cell count 3400 w/ 30% neutrophils, hematocrit 41, platelets 200,000. What should you advise her?
- A. She should have a bone marrow to rule out a bone marrow process causing neutropenia.
 - B. She should have serial blood counts to rule out cyclic neutropenia.
 - C. She should have chromosome analysis of her peripheral blood.
 - D. She should be evaluated for an elastase mutation.
 - E. She should go to France without any further evaluation.

Answer: E The normal neutrophil count is partially determined by ethnic background. African American males frequently have a neutrophil count of 1000 to 1500, and African American females may have counts that are even lower. Many may actually have counts below 1000. With a total neutrophil count of 1120, a normal hematocrit and platelet count, and an unremarkable history and physical examination, the patient should be diagnosed with constitutional neutropenia. This requires no further evaluation, although if DARC testing is available, confirming she is Duffy negative will confirm the diagnosis. The patient should be reassured that these counts are normal for her and present no undue risk. She should leave for France as planned. (See Ethnic and Benign Familial [Constitutional] Neutropenia.)

2. A 1-month-old baby boy presents with fever and cough and is found to have pneumonia associated with severe neutropenia. His parents have normal blood counts but had lost a baby girl at age 3 months under similar circumstances 2 years before. Which of the following statements is *not* true?
- A. The patient likely has a mutation in neutrophil elastase.
 - B. The child should be treated with granulocyte colony-stimulating factor (G-CSF).
 - C. The child is at risk for developing myelodysplastic syndrome and acute myeloid leukemia (MDS/AML).
 - D. If the child survives, his offspring will probably have normal neutrophil counts.
 - E. The child's white blood cell count likely has a 21-day cycle in and out of the normal range.

Answer: A This child has a disease that is apparent in neither parent but has a sibling that died of the same disease. This is consistent with an autosomal recessive form of severe congenital neutropenia (SCN). SCN related to neutrophil elastase mutation is an autosomal dominant disorder. Cyclic neutropenia is a milder autosomal dominant disorder, also due to mutations in *ELANE*; it is clinical mild and rarely presents in infancy. Although it can appear sporadically, the occurrence in a sibling makes that virtually impossible. This case is most consistent with Kostmann syndrome, which is due to mutations in the *HAX1* gene. Because it is a very rare recessive disorder, if the child lives to adulthood and has offspring, they will be obligate heterozygotes and, like the patient's parents, will have normal counts. Like patients with dominantly inherited SCN associated with neutrophil elastase mutations, these patients respond to G-CSF and have an increased risk for developing MDS/AML. (See Severe Congenital Neutropenia.)

3. A 45-year-old man presents to the emergency department after a motor vehicle crash. He is afebrile with a blood pressure of 160/95 mm Hg and a pulse of 110 beats per minute. He has several scrapes and bruises, but no major injuries. Admission complete blood count reveals: white blood cell count 16,000, hematocrit 45, and platelets 280,000. What is the most likely explanation for his leukocytosis?
- A. Acute bacterial infection
 - B. Undiagnosed chronic myelogenous leukemia
 - C. Stress-induced demargination of neutrophils
 - D. Cytokine release stimulating increased marrow production and release of neutrophils
 - E. Unsuspected splenic rupture

Answer: C Acute stress is commonly associated with leukocytosis. Acute leukocytosis in almost any setting occurs by demargination, in this case in response to the release of catecholamines during the stress of the accident, also causing his tachycardia. Cytokine-induced marrow proliferation and release of neutrophils reflect more chronic inflammation and could not have occurred in less than about a week. Unsuspected splenic rupture would likely lead to hypotension and shock. There is no reason to consider a diagnosis of chronic myeloproliferative disease or sepsis in the absence of other evidence for a secondary condition. The patient should have his counts rechecked in several days or weeks to rule out any other pathology. (See Stress.)

4. A 3-year-old child presents with recurrent infections and a diagnosis of Chédiak-Higashi syndrome (CHS) is made. Which of the following is *not* true of his disease?

- A. He is likely to have associated nystagmus.
- B. His sibling has a 50% chance of having the disease.
- C. He is likely to have abnormal neutrophil granules.
- D. He is likely to develop hemophagocytic syndrome.
- E. He is likely to have a defect in skin pigmentation.

Answer: A CHS is a generalized disorder of granule formation caused by abnormalities in the *LYST* gene, which is required for the correct trafficking of proteins into granules. Consequently, patients with CHS have other defects associated with abnormal granule formation, including oculocutaneous albinism, with decreased pigmentation and nystagmus, and abnormal-appearing neutrophil granules. As the disease is an autosomal recessive disorder, the heterozygous parents are usually totally unaffected, and siblings have a 25% chance of inheriting the disease. Patients with CHS often have a terminal phase of the disease associated with the development of hemophagocytic syndrome, manifesting as fever, splenomegaly, and pancytopenia, often as a result of Epstein-Barr virus infection. (See Other Congenital Syndromes with Associated Neutropenia.)

5. A 1-month-old infant presents with a temperature of 103° F and a white blood cell count (WBC) of 90,000. He has a history of delayed umbilical cord separation, poorly healing skin lesions, recurrent otitis media, and failure to thrive. He is admitted to the hospital, where he is documented to have methicillin-resistant *Staphylococcus aureus* (MRSA). He is placed on appropriate antibiotics, but he remains febrile, and his WBC is persistently elevated in the 80,000 to 100,000 range. This patient is likely to have a mutation in which of the following?

- A. *ELANE*
- B. *HAX1*
- C. Integrin receptor β chain
- D. *LYST*
- E. *G-CSFR*

Answer: C The child has a congenital disorder of neutrophils that results in leukocytosis. The diagnosis is leukocyte adhesion deficiency. This disease arises from defects in leukocyte adhesion to endothelium. It can arise from defects in the integrin receptor common β chain (LAD-1), with loss of expression of leukocyte function-associated antigen 1 (LFA-1), C3bi receptor, and gp150;95, leading to a failure to ingest and kill microbes opsonized by C3bi. It can also arise from an abnormality of selectin glycosylation (LAD-2). *ELANE* and *HAX1* mutations are causes of severe congenital neutropenia, and affected patients present with profound neutropenia. *LYST* mutations are the cause of Chédiak-Higashi syndrome, which is also associated with neutropenia. Congenital *G-CSFR* mutations are very rare, although two or three patients in the literature have been described to have such mutations as the basis for G-CSF-resistant severe congenital neutropenia. More commonly, *G-CSFR* mutations are somatic mutations that arise in patients with severe congenital neutropenia and may be a harbinger of the development of myelodysplastic syndrome or acute myeloid leukemia. (See Leukocyte Adhesion Deficiency.)

1. Which of the following is the most likely diagnosis in a patient with a 4-cm firm, nubby, nontender right lower cervical lymph node in an otherwise well 26-year-old female?

- A. Infectious mononucleosis
- B. Systemic lupus erythematosus (SLE)
- C. HIV infection
- D. Hodgkin lymphoma
- E. Cat-scratch disease

Answer: D When lymphadenopathy occurs in mononucleosis, HIV infection, or SLE, it tends to be generalized. The lymphadenopathy of cat-scratch disease can mimic that of a lymphoproliferative disorder but tends not to be as large and firm as in the case described here. Hodgkin lymphoma is the most likely diagnosis among these choices in an otherwise healthy young patient with a single prominent and firm enlarged node. (See Differential Diagnosis under Lymphadenopathy.)

2. After splenectomy, in addition to Howell-Jolly bodies, a peripheral smear is most likely to show which of the following?

- A. Thrombocytosis
- B. Toxic granulation of the neutrophils
- C. Spherocytes
- D. Dutcher bodies
- E. Nucleated red blood cells

Answer: A A reactive thrombocytosis is often seen after splenectomy, and it may persist for months or years. Toxic granulations in neutrophils are unrelated to removal of the spleen; they are seen in infections and inflammatory states regardless of spleen status. The other morphologic findings in blood cells are not modified according to whether or not there is an intact spleen. (See Laboratory Evaluation under Splenomegaly; also see Figure 168-1.)

3. Lymph node enlargement would be unusual in a patient with which of the following?

- A. Follicular lymphoma
- B. Tuberculosis
- C. Castleman disease
- D. Waldenström macroglobulinemia
- E. Multiple myeloma

Answer: E Localized or disseminated lymphadenopathy can be caused by malignant lymphoproliferative diseases (including follicular lymphoma and Waldenström macroglobulinemia; benign proliferative diseases of the immune system (including Castleman disease); and infections by bacteria, mycobacteria (including tuberculosis, fungi, chlamydia, parasites, and viruses). In contrast, multiple myeloma is a plasma cell dyscrasia (as opposed to Waldenström macroglobulinemia, which is actually a malignant lymphoproliferative disorder associated with a paraprotein) and is not characterized by lymphadenopathy. (See Differential Diagnosis under “Lymphadenopathy.”)

4. Fine-needle aspiration (FNA) of a lymph node is a good way to diagnose which of the following?

- A. Castleman disease
- B. Hodgkin lymphoma
- C. Sarcoidosis
- D. Metastatic tonsil carcinoma
- E. Post-transplantation lymphoproliferative disorder

Answer: D FNA is a popular and usually accurate means of diagnosing an infection or carcinoma involving a lymph node, like metastatic tonsil carcinoma. However, unequivocal diagnosis and histopathologic subtyping of lymphomas (including Hodgkin and non-Hodgkin lymphoma, such as post-transplantation lymphoproliferative disorder) or granulomatous disease (such as the noncaseating granulomas of sarcoidosis) require cutting needle or excisional lymph node biopsy, which preserves histologic architecture. (See Interventional Evaluation under Lymphadenopathy.)

5. Splenectomy early in life makes one particularly vulnerable to which of the following?

- A. Pneumococcal sepsis
- B. Bacterial endocarditis
- C. Salmonella sepsis
- D. Herpetic encephalitis
- E. Severe influenza

Answer: A Splenectomy early in life makes individuals particularly susceptible to sepsis with encapsulated organisms such as *Streptococcus pneumoniae*. However, there is little if any strong evidence for susceptibility to overwhelming systemic infections with other types of bacteria or viruses. This is the rationale for the recommendations for vaccination against *S. pneumoniae* and possibly also *Haemophilus influenzae* and *Neisseria meningitidis* before splenectomy. (See Definition under Splenomegaly.)

1. What is the probable diagnosis of an 8-year-old boy with severe dermatitis, recurrent bacteria skin infections, and pneumonia for evaluation of immunodeficiency? Initial tests reveal normal complete blood count and platelets, 40,000 IU of immunoglobulin E (IgE), and normal IgA, IgM, and IgG levels.

- A. Familial Mediterranean fever
- B. Chédiak-Higashi syndrome
- C. Hyper-IgE syndrome
- D. Chronic granulomatous disease
- E. Leukocyte adhesion deficiency

Answer: C This patient has recurrent bacterial infections and pneumonia, which suggest the possibility of an immunodeficiency. Significant levels of IgE present with normal complete blood count and platelets indicate hyper-IgE syndrome. Genetic testing of the *STAT3* gene can be used to confirm diagnosis. Good prognosis seen in patients with administration of antibiotics, antifungal prophylaxis, and IgG infusions.

2. A 3-year-old girl with abnormally light pigmentation of the hair and skin has a history of recurrent respiratory infection. Blood smear shows giant cytoplasmic granules and low neutrophil counts. What is the mostly likely diagnosis?

- A. Chédiak-Higashi syndrome (CHS)
- B. Specific granule deficiency
- C. Chronic granulomatous disease
- D. Interferon- γ receptor-1 defect
- E. Myeloperoxidase deficiency

Answer: A The low neutrophil count is an indication of neutropenia, in addition to giant cytoplasmic granules in the blood smear, suggesting CHS. Significant indication of CHS includes partial albinism as seen in patients light pigmentation and defects in bacterial killing and chemotaxis, which can be confirmed through neutrophil function testing. Infections can be treated with prophylactic antibiotics.

3. A 6-year-old girl has a history of recurrent otitis and hemolytic anemia. Testing indicates significant excretion of 5-oxoproline in the urine and low amounts of glutathione synthetase in red blood cells. What is the mostly likely diagnosis?

- A. Glutathione synthetase deficiency
- B. Macrophage activation syndrome
- C. Chronic granulomatous disease
- D. Myeloperoxidase deficiency
- E. Hyper-IgE syndrome

Answer: A This patient's low levels of glutathione synthetase suggest a mild form of glutathione synthetase deficiency. Diagnosis can be confirmed with 5-oxoproline buildup and mutations in the *GSS* gene. Antioxidant supplementations are suggested for treatment.

4. The attraction of neutrophils and other white blood cells to an inflammatory site is called which of the following?

- A. Chemotaxis
- B. Margination
- C. Diapedesis
- D. Phagocytosis
- E. Extracellular trap

Answer: A Chemotaxis is the attraction and oriented movement of neutrophils to an inflammatory site after the release of chemoattractants.

5. A 15-month-old female infant is admitted for recurrent deep skin infections. Flow cytometry confirmed deficiency in vitamin B12. Blood smear displays bilobed neutrophil nucleuses. What is the likeliest diagnosis?

- A. Specific granule deficiency
- B. Chronic granulomatous disease
- C. Interferon- γ receptor-1 defect
- D. Myeloperoxidase deficiency
- E. Macrophage activation syndrome

Answer: A Morphologically altered neutrophils are a strong indication of specific granule deficiency. This condition usually manifests during infancy, including recurrent skin infections and vitamin B12 deficiency. Treatment options include parenteral antibiotics and drainage of infections.

Ch / 170 EOSINOPHILIC SYNDROMES

1. A 40-year-old man presents with blood eosinophilia and rash. The chest radiograph is normal, and the blood eosinophil count is 5000 cells/mm³ on two occasions over the course of 1 month. He has no history of allergies and no risk factors for parasite infection. A bone marrow biopsy shows elevated eosinophils with no blasts. The next step would be which of the following?

- A. Lymphocyte phenotyping and serum immunoglobulin levels
- B. Determining the presence of the *FIP1L1-PDGFR* fusion gene
- C. Following the eosinophil count over the course of 6 months to document true hypereosinophilia
- D. Determining IgE and HIV titers
- E. All of the above

Answer: B The patient is presenting with classic signs of hypereosinophilic syndrome and should be evaluated for *FIP1L1-PDGFR* because its presence would lead to imatinib therapy. Delay of 6 months exposes the patient to the potentially unnecessary risk for eosinophilia-mediated organ damage.

2. An asthmatic young man presents with progressive difficulty swallowing that is refractory to proton pump inhibitor therapy for the past 2 months. The peripheral blood count and differential are normal, specifically without eosinophilia. Which of the following is true regarding eosinophilic esophagitis?

- A. It is not indicated because the patient does not have blood eosinophilia.
- B. It should only be considered after repeating the blood eosinophil count over a period of time.
- C. It can be assumed and treated with anti-IL-5 therapy.
- D. It should be ruled out with a referral to a gastroenterologist for endoscopic evaluation.
- E. It should only be considered after checking for the presence of the *FIP1L1-PDGFR* fusion gene.

Answer: D Eosinophilic esophagitis is a tissue-specific eosinophilic disorder that can only be diagnosed by endoscopic biopsy and does not have to be accompanied by peripheral blood eosinophilia.

3. A middle-age women presents with progressive weight loss and diarrhea and is found to have blood eosinophil count of 5000 cells/mm³. She is a nonatopic individual and has recently returned from a trip to Brazil. Which of the following would be the next step in evaluating this person?

- A. Bone marrow analysis and cytogenetics
- B. HIV titer
- C. Stool culture and evaluation for parasites
- D. Colonoscopy
- E. Serologic testing for inflammatory bowel disease

Answer: C The patient has an acute presentation of eosinophilia following travel to a region likely endemic for parasites such as schistosomiasis. The next step would be a stool evaluation for parasites.

4. An 18-year-old male presents with a generalized erythematous eruption and peripheral blood eosinophilia of 2500 cells/mm³. The history is significant for recent antibiotic use for a cellulitis in the leg. The cellulitis has not improved despite 10 days of antibiotics. The next step in evaluating this patient would include consideration of which of the following?

- A. The patient likely has a simple drug allergy and should switch antibiotics.
- B. The patient may have an underlying hypereosinophilic syndrome and should undergo skin biopsy, particularly at the site of the cellulitis.
- C. The patient should have a chest and abdominal computed tomography scan to rule out solid tumor malignancy.
- D. Referral should be made to a cardiologist to rule out cardiac involvement.
- E. It is critical to rule out parasitic infection as the next step.

Answer: B The most common organ involved in hypereosinophilic syndrome is the skin. Although this patient may have a drug reaction, the persistent cellulitis is concerning for an underlying primary inflammatory process.

5. A well-appearing 60-year old woman is found to have persistent blood eosinophil counts of 3500 cells/mm³. She denies risk factors for parasite infection, is nonatopic, and has started no new medication, although she has been taking a statin and antihypertensive agent for several years. Which of the following considerations should take place?

- A. Because this is a well-appearing female patient, there is little concern for hypereosinophilic syndrome.
- B. Complete work-up is indicated that includes a computed tomography scan of the abdomen and bone marrow analysis.
- C. Consideration of drug-induced eosinophilia is not appropriate because the patient has not started any new medications.
- D. The patient should be simply followed by serial complete blood counts because she is clinically well.
- E. A stool sample for ova and parasite should be the next step.

Answer: E The next logical step would be ruling out an infection. Serial complete blood counts should be performed but not in isolation because it has already been established that the patient's eosinophilia is persistent.

1. You are asked to clear a 48-year-old man for elective surgery for a herniated disc because he told his surgeon that he has a history of some kind of “blood problem.” The patient tells you he bled heavily one day after a dental extraction 5 years ago, requiring blood transfusions in his local hospital’s emergency department. He also recalls his parents telling him that he “almost died” of bleeding after a tonsillectomy in early childhood. There have been no other bleeding problems, even though he was an All-American soccer player in college and proudly says that he didn’t bruise any more than his teammates. Family history is negative for bleeding except for his maternal grandfather, who had serious postoperative bleeding after coronary artery bypass graft surgery. The patient’s screening coagulation test results now are normal: platelets = 380,000; prothrombin time (PT) = 11.4 (international normalized ratio [INR] = 1.0); partial thromboplastin time (PTT) = 27.5. What would you do now?
- A. Clear him for surgery with close postoperative observation for bleeding.
 - B. Order a bleeding time and platelet function tests.
 - C. Order factor VIII and factor IX levels.
 - D. Order liver function tests.
 - E. Order von Willebrand factor (VWF) multimer analysis.

Answer: C The type of bleeding complications this patient describes (i.e., delayed, deep bleeding, especially at oropharyngeal sites with surgery) is more characteristic of a coagulation factor defect than a platelet-vascular defect. His family history is suggestive of an X-linked inherited coagulopathy, with his mother being the silent carrier. Factor VIII deficiency (classic hemophilia) and factor IX deficiency fit that description. The PTT is not a sensitive screening test to pick up less severe forms of a coagulopathy (i.e., when the factor level is >25%), so *mild* hemophiliacs (with either factor VIII or IX deficiency) may have a normal PTT and yet still have serious bleeding complications when provoked with surgery. Therefore, factor VIII and IX levels must be obtained here to rule out the mild hemophilia, which would require prophylactic preoperative (as well intraoperative and postoperative) replacement therapy. The bleeding time, a method to test the integrity of platelet-vascular interactions, is now largely an obsolete test; and the kinds of bleeding problems this patient describes (as well as the notable absence of pathologic bruising with trauma) argues strongly against a qualitative platelet abnormality. Liver function tests could be done but are unlikely to shed additional light on this diagnostic problem; furthermore, this patient appears to have an inherited, not acquired coagulopathy. The possibility of von Willebrand disease is not unreasonable (even though it is usually autosomal dominant), although, again patients with von Willebrand disease tend to bleed superficially like patients with platelet problems. In any case, multimer analysis is not the first step to diagnosing von Willebrand disease: it should be preceded by a von Willebrand panel to assay levels of functional VWF, antigenic VWF, and factor VIII activity.

2. A 68-year-old man with coronary artery disease, diabetes mellitus, hypertension, and a history of stroke followed by seizures is now 3 days after an uncomplicated coronary artery bypass graft (CABG) surgery, and you are asked to consult for severe thrombocytopenia. The patient is on multiple medications for his chronic conditions and is now on postoperative subcutaneous heparin for thromboprophylaxis. There have been no bleeding problems postoperatively, and physical examination shows no signs of bleeding from external orifices and no ecchymoses or petechiae. The platelet count today is 5000, which triggered the STAT consult; it had been previously normal, including a count of 280,000 yesterday. Which of the following should be the first step?
- A. Examine the peripheral blood smear for platelet clumping.
 - B. Stop heparin.
 - C. Stop heparin and all other medications.
 - D. Order STAT platelet transfusions.
 - E. Take a thorough history and do a comprehensive physical examination.

Answer: A The first step is to promptly determine whether the apparently sudden drop in platelet count is real or artifactual. The abrupt drop (when counts were normal as recently as 1 day ago), accompanied by the striking absence of symptoms or signs of bleeding in this patient raises a high level of suspicion for "pseudothrombocytopenia." Seeing large clumps of platelets on the peripheral smear, which should be examined by the hematologist, would confirm the suspicion, which should be then promptly documented by ordering repeat platelet counts in both the customary purple-top tube containing EDTA as the anticoagulant along with tubes containing other anticoagulants (heparin or citrate). (The platelet count in the EDTA tube should be again very low, but not in blood collected into test tubes with the other anticoagulants.) Occasionally, pseudothrombocytopenia occurs as a result of the presence of a nonphysiologic "cold agglutinin," which clumps platelets in the test tube while sitting at room temperature before counting. This can be ruled out by having the laboratory do simultaneous platelet counts on a tube kept at 37° C versus one that has been intentionally left standing at room temperature: the former should have a normal platelet count if this is the case. These findings represent pseudothrombocytopenias in which the platelet counts are artifactually low and of no clinical consequence. These tests can be all done very quickly without stopping important medications, including heparin, and before undertaking further work-up and treatment of the thrombocytopenia if they remain necessary.

3. Which of the following statements is correct regarding the relationship between cancer and thrombosis?

- A. In a patient being treated for gastric cancer, secondary prevention following a first episode of venous thromboembolism is best provided by warfarin for 3 to 6 months at doses to target an international normalized ratio of 2.0 to 3.0.
- B. A first episode of apparently unprovoked deep vein thrombosis in a previously healthy individual requires comprehensive search for an occult malignancy, including computed tomography of the chest, abdomen, and pelvis.
- C. Pulmonary embolism in a patient being actively treated for cancer requires the placement of an inferior vena cava (IVC) filter to prevent recurrence.
- D. A patient with breast cancer who completed treatment 6 months ago and is now in complete remission, with no evidence of disease, is not at increased risk for venous thromboembolism.
- E. In a previously healthy individual, the spontaneous development of extensive IVC thrombosis is highly suggestive of an occult renal cell carcinoma.

Answer: E IVC thrombosis, a rare and dramatic form of venous thrombosis that can extend into the right atrium, is associated with renal cell carcinoma. Other characteristic (but not diagnostic) cancer-associated thrombosis syndromes include Budd-Chiari syndrome (hepatic vein thrombosis) or portal vein thrombosis in patients with myeloproliferative neoplasms, and superficial, migratory thrombophlebitis (Trousseau syndrome) with occult cancers of the gastrointestinal tract and pancreatic cancer. Subcutaneous low-molecular-weight heparin is superior to dose-adjusted warfarin for secondary prophylaxis after an episode of venous thromboembolism in a cancer patient, even when in remission, and it should be continued indefinitely. Although the incidence of occult malignancy in a previously healthy person who presents with unprovoked venous thromboembolism is definitely increased, most experts agree that a comprehensive history and physical examination, stool for occult blood, chest radiograph, blood counts and basic chemistries, and a mammogram in women is a sufficient initial screen for occult cancer, as long as any abnormalities picked up on that screen are more aggressively pursued. Increased risk for thrombosis in a patient with cancer continues for months or even years after complete remission has been achieved. An IVC filter is inadequate to prevent recurrent pulmonary embolism in patients with or without cancer.

1. You are asked to see a patient who had coronary bypass surgery 6 days ago. The patient has abruptly developed a cold right foot, and his platelet count decreased from 350,000/ μ L yesterday to 155,000/ μ L today. He is afebrile, and his only medication is subcutaneous heparin for deep vein thrombosis (DVT) prophylaxis. You are suspicious that the patient may have heparin-induced thrombocytopenia. What should you recommend?

- A. Discontinue heparin and start argatroban.
- B. Discontinue heparin and observe platelet trend.
- C. Discontinue heparin and start aspirin.
- D. Send heparin-PF4 enzyme-linked immunosorbent assay (ELISA) and base treatment on results.
- E. Change heparin to low-molecular-weight heparin.

Answer: A Stop the heparin and administer argatroban. This patient developed a probable thrombosis in his foot and had a greater than 50% decrease in his platelet count 6 days after starting to receive heparin. The time course and the magnitude of the decrease in the platelet count, along with the new thrombosis, places this patient at very high risk for the diagnosis of heparin-induced thrombocytopenia and at a very high immediate risk for a recurrent thrombotic event, even if the heparin was discontinued (ruling out answers B, C, and D). Consequently, this patient needs to be started on an alternative anticoagulant that is different enough from heparin to not be recognized by the immune response directed against heparin (ruling out answer E). Aspirin alone is not sufficient to prevent recurrent thrombi. The only acceptable approach would be to stop the heparin and to immediately start Argatroban. See Heparin-induced Thrombocytopenia, Table 172-1, Figure 172-2, and reference 2.

2. You have just met a patient with a platelet count of 115,000/ μ L. She has no other medical problems, and the remainder of her complete blood count (CBC) and blood smear are normal. Review of her old CBC indicates that her platelet count 1 year ago was 120,000/ μ L. What should you recommend?

- A. Refer patient for bone marrow biopsy.
- B. Repeat CBC in 1 week.
- C. Repeat CBC in several months.
- D. Analyze patient for antiplatelet antibodies.
- E. Initiate folate and B12 therapy.

Answer: C Repeat CBC in several months. The patient has asymptomatic and stable mild thrombocytopenia. Her platelet count is probably at the lower end of the normal platelet count distribution, although she has a small chance of having mild idiopathic thrombocytopenic purpura (ITP) (see reference 1). Because her white and red blood cell counts are normal, and her peripheral blood smear is normal, there is no need for a bone marrow biopsy. There is no indication to repeat her CBC in a week because her platelet count is already documented as having been stable for the past year. Antiplatelet antibody assays have inadequate sensitivity and specificity to be clinically useful. In the absence of anemia and a documented deficiency of folate or B12, there is no indication for the supplementation of these vitamins. See Figure 172-1 for further details on evaluating patients with chronic thrombocytopenia.

3. You are managing a patient with ITP, who typically has a platelet count of 60,000/ μ L to 90,000/ μ L. Today, she complains of symptoms consistent with an upper respiratory infection. Her CBC demonstrates that her platelet count is 42,000/ μ L today but is otherwise normal. Her blood smear is normal. She is on no new medications, and on physical examination her nares appear congested, but she has no ecchymosis, petechiae, or splenomegaly. What should you recommend?

- A. Refer patient for bone marrow biopsy.
- B. Repeat CBC in 1 week.
- C. Start corticosteroid therapy.
- D. Start intravenous immunoglobulin.
- E. Start romiplostin.

Answer: B Repeat CBC in 1 week. The patient has an exacerbation of her ITP that is potentially a result her viral syndrome. Her otherwise normal CBC and blood smear exclude the need to consider diagnoses that would be demonstrated on a bone marrow biopsy (answer A). In the absence of excessive bleeding or a platelet count of less than 30,000/ μ L, there is no indication for therapy (excluding answers C, D, and E.) If her platelet count in a week continues to decrease, she might require a brief course of an ITP therapy, such as corticosteroids. See Idiopathic (Immune) Thrombocytopenic Purpura and reference 4.

4. One week ago, you prescribed trimethoprim-sulfamethoxazole for a patient with cellulitis. Her cellulitis is now resolved, but you order a CBC because her leukocyte count was 13,500/ μ L last week. Today's CBC demonstrates that her leukocyte count is now 9,200/ μ L with a normal differential, her hemoglobin is 13.9 g/dL, and her platelet count is 77,000/ μ L. Looking back at the older laboratory results, you notice that this is the first time she has ever been thrombocytopenic. The patient has no symptoms or signs of excessive bleeding, and her spleen is not enlarged. Which of the following should you recommend?

- A. Corticosteroids
- B. Bone marrow biopsy
- C. Hospitalization of patient for close observation
- D. Discontinuing antibiotics and repeating CBC in 1 week

Answer: D Discontinue antibiotics and repeat the CBC in 1 week. The patient is asymptomatic and has an abrupt onset of moderate thrombocytopenia. Because her platelet count was normal a week ago, it makes it extremely likely that her thrombocytopenia is due to her exposure to a drug or infection (excluding answer B). Her current platelet count does not place her at a high risk for hemorrhage (excluding answers A and C.) See Drug-induced Thrombocytopenia and Table 172-3.

5. A patient is admitted with confusion and abdominal pain. She has a body temperature of 101.1° F, and her laboratory studies demonstrate the following: leukocyte count 4,400/ μ L, hemoglobin 10.5 g/dL, platelet count 11,000/ μ L, D-dimer 0.2 μ g/mL, and creatinine 1.1 mg/dL. The peripheral blood smear shows nucleated red blood cells and fragmented red blood cells (schistocytes). Which of the following should you recommend?

- A. Intravenous immunoglobulin
- B. Platelet transfusion
- C. Platelet transfusion and red blood cell transfusion
- D. Plasmapheresis
- E. Antibiotics

Answer: D Plasmapheresis. The patient has thrombocytopenia and anemia associated with schistocytes on her blood smear. This indicates that she has a microangiopathic hemolytic anemia. The presence of fever and neurologic symptoms suggests that the patient's diagnosis is thrombotic thrombocytopenic purpura (TTP). The normal D-dimer excludes the other likely diagnosis of disseminated intravascular coagulation. TTP requires immediate treatment with plasmapheresis. This treatment alone will correct the problem and increase the platelet count (this excludes answers A and B). Her anemia is mild, so there is no indication for red blood cell transfusion at this time (answer C). Because TTP frequently causes fever, there is no indication for antibiotics at this time (answer E). See Thrombotic Thrombocytopenic Purpura and Figure 172-4.

1. A 40-year-old woman complains of easy bruising and menorrhagia present for a few years. Bruises have mainly occurred on the lower extremities, often after recollected minor trauma, and typically have been small (<1-3 cm in diameter) and without induration (hematomas). Her menses have been heavier in recent years but without passage of blood clots, and there is no history of anemia. A previous pregnancy and full-term vaginal delivery were uncomplicated by bleeding with delivery or postpartum. During childhood, she had occasional nosebleeds that did not require medical attention. She has not undergone surgical challenges nor had dental extractions or significant injuries. Currently, she is not using oral contraceptive or iron supplementation, nor taking aspirin or other nonsteroidal antiinflammatory drug (NSAIDs). Family history review is negative for bleeding disorder. Physical examination discloses two small superficial bruises (1-2 cm diameter) on the lower extremities but is otherwise unremarkable, including no evidence of oronasal or skin telangiectasias nor unusual skin or joint laxity. Recent laboratory testing demonstrates normal complete blood count (CBC) results, including platelet and erythrocyte measurements, and normal prothrombin time (PT) and activated partial thromboplastin time (aPTT). From previous ABO blood group testing, she is known to have blood group O. Concerning additional evaluation for possible von Willebrand disease (VWD), which *one* of the following is the most appropriate recommendation for initial laboratory blood sample testing?

- A. Platelet function analyzer (PFA-100) closure time
- B. Von Willebrand factor (VWF) antigen (VWF:Ag)
- C. VWF:Ag and VWF ristocetin cofactor activity (VWF:RCo)
- D. VWF:Ag, VWF:RCo, and coagulation factor VIII activity (FVIII)
- E. VWF:Ag, VWF:RCo, FVIII, and VWF multimer analysis

Answer: D The medical and bleeding history review raises the possibility of a mild bleeding disorder such as VWD (that would not be excluded by normal CBC, PT, and aPTT test results). PFA-100 or bleeding time (BT) testing are not recommended for initial screening to detect or exclude VWD because they lack sufficient sensitivity and are nonspecific tests. The three recommended tests to screen for or exclude VWD are VWF:Ag, VWF:RCo, and coagulation FVIII. Abnormal results on one or more of these three tests may also help identify the subtype of VWD if present and its severity, and supplemental or follow-up VWD tests may be indicated for clarification. VWF multimer analysis is not recommended for initial screening for VWD unless there is high clinical suspicion of abnormal VWF multimers such as can occur in association with acquired Von Willebrand syndrome (AVWS).

2. The following blood plasma test results are obtained for the 40-year-old woman described in question 1.

VWF:Ag = 42% (reference range, 50%-200%)

VWF:RCo = 42% (reference range, 50%-200%)

FVIII = 60% (reference range, 55%-200%)

What is the most appropriate interpretation of these test results in the context of the clinical information?

- A. Type 1 VWD
- B. Possible type 1 VWD
- C. "Low VWF"
- D. Type 2A VWD
- E. B and C

Answer: E The mildly decreased levels of VWF:Ag and VWF:RCo (with low normal FVIII) suggest the possibility of mild type 1 VWD vs. "low VWF" such as can occur in apparently normal individuals with blood group O. The latter can have VWF levels as low as approximately 40% of mean normal. The patient's mild bleeding history (childhood nosebleeds not requiring medical interventions, ease of bruising with small bruises only, menorrhagia that apparently has not caused anemia or iron

deficiency, absence of other bleeding symptoms or events) is not definitive for VWD or another bleeding disorder at this time, although raising possibility of such. The concordant VWF:RCo and VWF:Ag levels (ratio, 1.0; reference range, ≥ 0.5 -0.7) are not suggestive of type 2A VWD. If clinical suspicion of VWD remains, it could be appropriate to repeat the VWD panel testing in the absence of conditions associated with elevation of baseline VWF and FVIII levels (see Table 173-3).

Nichols WL, Hultin MB, James AH, et al. Von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). *Haemophilia*. 2008;14(2):171-232.

American Society of Hematology. 2012 *Clinical Practice Guideline on the Evaluation and Management of von Willebrand Disease (VWD)*. www.hematology.org/policy/resources/guidelines/vwd.

3. A 47-year-old woman is establishing medical care, having recently relocated, and has a history of von Willebrand disease (VWD) but is otherwise apparently in good health. She is unsure of the specific diagnosis such as VWD subtype and is in the process of obtaining her previous medical records. She reports a lifelong bleeding tendency, including recurring nosebleeds that have sometimes required nasal packing or cautery, excessive bleeding with cuts or other minor trauma, and troublesome bleeding after a dental extraction (prolonged oozing managed with packing). Since menarche, she has had menorrhagia that was initially managed by oral contraceptive therapy beginning at age 15 years in association with the diagnosis of VWD. Her only successful pregnancy at age 38 years was managed by cesarean section supplemented with infusions of VWF-FVIII concentrate, and she did not have bleeding complications. Family history discloses that neither of her parents had a history of abnormal bleeding, nor did two brothers or one sister nor their progeny. Her son has had troublesome nosebleeds and tonsillar bleeding and has been diagnosed as having VWD; however, no additional details or laboratory test results are currently available. Her physical examination is essentially unremarkable, including no pallor.

Initial laboratory testing results include a normal complete blood count (CBC), prothrombin time (PT) and activated partial thromboplastin time (aPTT). A VWD test profile with reflexive supplemental VWF testing of plasma yielded these results:

VWF:Ag = 24% (reference range, 50%-200%)

VWF:RCo = <12% (reference range, 50%-200%)

FVIII = 34% (reference range, 55%-200%)

VWF-platelet binding activity (latex immunoassay screen) = 7% (reference range, 50%-200%)

VWF multimer analysis = abnormal, with absence of higher molecular weight multimers and increased abundance of lower-molecular-weight multimers (normal = "normal multimer distribution")

What is the most appropriate interpretation of the VWD profile test results in the context of the clinical information?

A. Type 1 VWD

B. "Low VWF"

C. Type 2A VWD

D. Type 2B VWD

E. Type 3 VWD

Answer: C The clinical history identifies a variety of mucocutaneous bleeding episodes lifelong and altogether yields an elevated bleeding history assessment "score" that is highly suggestive of hereditary or congenital VWD or a similar bleeding disorder. The family history of VWD (son) provides additional probability that the woman has VWD. Values for plasma VWF:Ag and FVIII are substantially decreased, and VWF:RCo is undetectably low, altogether consistent with VWD. The unmeasurably low value for VWF:RCo was reflexively evaluated using an automated immunoassay based on a latex-coupled monoclonal antibody to the VWF-platelet glycoprotein (GP) Ib binding domain to indirectly measure VWF-platelet binding activity and confirms a very low but measureable value (7%). The discordantly lower values for VWF:RCo activity and VWF "immunoactivity," relative to the higher value for VWF:Ag, yield decreased activity to antigen ratios (<0.5; reference range, ≥ 0.7 -0.8) and are indicative of a qualitative defect of VWF-platelet binding, consistent with types 2A, 2B, or 2M VWD.

Supplemental VWF multimer analysis demonstrates absence of higher-molecular-weight multimers consistent with types 2A or 2B VWD and not consistent with type 2M VWD (nor types 1 or 3 VWD). The blood platelet count (CBC) is normal, providing no suggestion of type 2B VWD (or platelet-type “pseudo-VWD”), conditions that typically manifest persisting or intermittent thrombocytopenia. However, supplemental testing would be indicated to definitively exclude these rare VWD subtypes: ristocetin-induced platelet aggregation (RIPA), including demonstration of no abnormal response to low-dose ristocetin.

Nichols WL, Hultin MB, James AH, et al. Von Willebrand disease (VWD): evidence-based diagnosis and management guidelines, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel report (USA). *Haemophilia*. 2008;14(2):171-232.

American Society of Hematology. 2012 Clinical Practice Guideline on the Evaluation and Management of von Willebrand Disease (VWD). <http://www.hematology.org/policy/resources/guidelines/vwd>.

4. A 64-year-old man has had intermittent gastrointestinal (GI) bleeding episodes (melena or hematochezia) for about 7 years, sometimes requiring red blood cell transfusions. Repeated upper and lower GI endoscopies and capsule imaging studies have failed to identify a source of bleeding. However, recently a capsule study and subsequent extended GI endoscopy identified several focal vascular ectasias (arteriovenous malformations) in the duodenum and proximal jejunum which were photoablated. He has not had other types or episodes of bleeding, including having undergone several surgical procedures (lithotripsy for nephrolithiasis, partial parathyroidectomy for hyperparathyroidism, dental extraction) before onset of the recurrent GI bleeding. There is no family history of a bleeding disorder. Additionally, the patient has a 13-year history of exertional dyspnea with occasional syncopal episodes and 5 years ago was diagnosed as having hypertrophic obstructive cardiomyopathy (HOCM) with aortic stenosis–like left ventricular outflow obstruction that has gradually worsened by clinical and echocardiographic assessments.

Recent hematologic testing included a normal complete blood count (CBC) and platelet count and normal prothrombin time (PT) and activated partial thromboplastin time (aPTT). A von Willebrand disease (VWD) test profile with reflexive supplemental von Willebrand factor (VWF) multimer analysis yielded these plasma test results:

VWF:Ag = 159% (reference range, 50%-200%)

VWF:RCO = 116% (reference range, 50%-200%)

FVIII = 119% (reference range, 55%-200%)

VWF multimer analysis = abnormal, with absence of the highest-molecular-weight multimers and no increased abundance of lower molecular weight multimers (normal = “normal multimer distribution”)

What is the most appropriate clinical diagnosis, considering the clinical and laboratory test results, including the VWD profile test results?

A. No evidence of VWD

B. Acquired Von Willebrand syndrome (AVWS)

C. Heyde’s syndrome

D. B and C

E. Type 2M VWD

Answer: D The clinical history identifies recurring GI bleeding for several years but no antecedent abnormal bleeding history nor family history of such, and suggests the possibility of focal (GI) anatomic abnormalities or an acquired bleeding diathesis. Recent GI endoscopy has identified small bowel vascular ectasias or angiodysplasias (arteriovenous malformations) as the probable anatomic source of GI bleeding. The association of GI bleeding and severe aortic stenosis is known as Heyde’s syndrome. Many patients with Heyde’s syndrome have GI angiodysplasias (AVMs), as well as acquired abnormalities of VWF (selective absence of the highest-molecular-weight VWF multimers) that reflects effects of the abnormally high blood shear flow stress associated with severe aortic stenosis. It is thought that the VWF abnormality predisposes to bleeding from GI AVMs and may also contribute to AVM formation (dysregulated angiogenesis) and results in AVWS, which is a bleeding propensity reflecting acquired VWF changes.

In this context, answer D (Heyde's syndrome + AVWS) is the most appropriate diagnosis. However, because the patient has HOCM rather than classic aortic valvular stenosis, one might consider the diagnosis to be "Heyde's syndrome variant" or a similar appellation. Although the patient's levels of VWF:RCo and VWF:Ag are normal and adequately concordant (ratio, 0.73; reference range, ≥ 0.7), it is only the VWF multimer analysis that allows detection of the VWF abnormality. Alternative evolving methods for measuring VWF activity may have greater sensitivity for detecting subtle VWF multimeric abnormalities (abnormal VWF activity to antigen ratio) compared with the VWF:RCo assay. This vignette is based on a published case; the patient underwent cardiac septal myectomy and has remained free of GI bleeding for more than 7 years of follow-up.

Blackshear JL, Schaff HV, Ommen SR, et al. Hypertrophic obstructive cardiomyopathy, bleeding history and acquired von Willebrand syndrome: response to septal myectomy. *Mayo Clin Proc.* 2011;86:219-224.

5. A 75-year-old man is referred for evaluation of an 18-month history of recurring severe nosebleeds and an earlier episode of gastrointestinal (GI) bleeding. He had three episodes of severe and prolonged nosebleeds requiring nasal packing or cautery, and red blood cell transfusions were given on one occasion. One year before the onset of nosebleeds, he had melena that was evaluated with upper and lower endoscopies that identified arteriovenous malformations (AVMs) in the stomach and duodenum that were cauterized, and later a GI capsule imaging study identified a possible jejunal AVM. He had also noted some increased bruising that improved after stopping prophylactic aspirin. The patient has not previously experienced abnormal bleeding and had several surgical challenges, including bilateral knee replacements, radical prostatectomy, inguinal hernia repair, and childhood tonsillectomy and adenoidectomy. His general health has otherwise been relatively good (treated hypertension and hyperlipidemia). Family history is not suggestive of a hereditary or congenital bleeding diathesis. Physical examination is unremarkable for age.

Initial laboratory evaluation identified borderline low blood hemoglobin (12.2 g/dL) with normocytic erythroid indices, and normal blood platelets and leukocyte count and differential. Serum ferritin was decreased (12 mcg/L; reference range, 24-336 mcg/L). Hemostatic testing included normal prothrombin time (PT), thrombin time, and fibrinogen level, however the activated partial thromboplastin time (aPTT) was mildly prolonged (48 sec; reference range, 26-36 sec), and a 1 : 1 mixing study with normal plasma (nonincubated) demonstrated correction. Coagulation factor activity assays demonstrated substantially decreased factor VIII (FVIII, 8%; reference range, 55%-200%), but factors IX, XI and XII were normal, as was a factor XIII screening assay. Supplemental testing was negative for a time-dependent FVIII inhibitor. Von Willebrand disease (VWD) testing demonstrated markedly decreased plasma VWF:Ag (9%; reference range, 50%-200%) and undetectably low VWF:RCo (<12%; reference range, 50%-200%), with supplemental VWF immunoactivity assay confirming low value (11%; reference range, 50%-200%). VWF multimer analysis revealed barely detectable VWF multimers, however, all multimeric species appeared to be present with no reduction of higher-molecular-weight multimers.

Considering a preliminary diagnosis of probable acquired Von Willebrand syndrome (AVWS), which *one* of the following investigations would be most likely to uncover the etiologic cause of AVWS?

- A. VWF inhibitor testing
- B. Transthoracic echocardiography (TTE)
- C. Serum thyroid stimulating hormone (TSH) assay
- D. Serum protein electrophoresis and immunoelectrophoresis
- E. Bone marrow biopsy

Answer: D The broad differential diagnostic categories of disorders pathophysiologically associated with AVWS include (1) antibodies to VWF, especially monoclonal gammopathies (e.g., monoclonal gammopathy of undetermined significance [MGUS], myeloma, macroglobulinemia) and less commonly autoimmune disorders such as (systemic lupus erythematosus [SLE]); (2) lymphoproliferative disorders such as chronic lymphocytic leukemia (CLL) and lymphoma; (3) myeloproliferative disorders associated with marked thrombocytosis (e.g., essential

thrombocythemia, polycythemia vera); (4) aberrant VWF binding to tumor cells (e.g., certain lymphoproliferative disorders or rarely other tumors); (5) cardiovascular disorders associated with shear-induced proteolysis of VWF, including aortic valvular stenosis, hypertrophic obstructive cardiomyopathy (HOCM), ventricular septal defect, ventricular assist devices (VADs), and so on; (6) decreased VWF synthesis such as in association with hypothyroidism; and (7) certain drugs (e.g., ciprofloxacin, valproic acid, hydroxyethyl starch). Considering the patient's age, essentially normal CBC findings, overall medical history, and the physical examination without evidence of hepatosplenomegaly or lymphadenopathy, nor aortic stenosis or similar conditions, MGUS would be high on the list of conditions to consider and evaluate. In this case, the patient was found by serum protein electrophoresis and immunoelectrophoresis to have a monoclonal IgG kappa monoclonal protein along with increased free

kappa light chain in the serum, but total serum IgG level was normal, all consistent with MGUS in the overall clinical context (Chapter 187). Monoclonal immunoglobulins can have specificity for VWF and cause clearance of immune complexes, typically without inhibiting VWF function, and causing very low VWF levels with secondary deficiency of FVIII. Inhibitors of VWF activity (VWF:RCo), either paraproteins or autoantibodies, are rarely detected by currently available testing, and VWF inhibitor test results were negative. Essentially normal CBC findings (except for mild anemia reflecting iron deficiency), together with physical examination, effectively excluded other causes of AVWS, including myeloproliferative or other lymphoproliferative or malignant disorders. The patient was not receiving drugs that can cause AVWS.

This patient received a trial infusion of VWF-FVIII concentrate (50 VWF:RCo units/kg body weight), and testing of blood samples showed transient normalization of VWF and FVIII levels that returned to baseline values within 24 hours, suggesting shortened survival. A trial infusion of intravenous immunoglobulin (IVIG, 1 g/kg body weight) was given, and serial testing of blood samples documented normalization of VWF and FVIII levels within 24 hours, with sustained normal levels for more than 5 days. It was recommended that either the former or the latter of these treatments be considered for future episodes of serious bleeding. There have been several case reports and small case series describing that infusion of IVIG can transiently normalize decreased VWF and FVIII levels in persons with IgG isotype monoclonal gammopathies.

1. A 7-month-old boy with severe hemophilia A, who is receiving daily postoperative factor replacement for major surgery 10 days ago, has developed several large painful hematomas over his extremities. Despite factor replacement, his hematomas have not improved. Which of the following approaches is most appropriate for this child?

- A. Draw trough factor VIII (before next dose), activated partial thromboplastin time (aPTT) mix, and anti-factor VIII.
- B. Draw peak factor VIII (after the next dose), aPTT mix, and anti-factor VIII.
- C. Draw aPTT, aPTT mix, and anti-factor VIII.
- D. Draw random factor VIII.
- E. Dose with 100% factor VIII and apply ice to hematomas.

Answer: B This child likely has developed an inhibitor because there was long duration factor early in life, and despite ongoing factor treatment, hematoma formation has occurred, indicating lack of response. To determine whether an inhibitor is present, the simplest approach is to draw a factor VIII level just after a 100% dose (i.e., peak); in the case of an inhibitor, the factor VIII level will be neutralized and lower than expected. A random factor VIII could also be drawn, but because children have a large volume of distribution, it is not as helpful as a peak factor VIII. Prolongation of both the aPTT and aPTT mix confirms the presence of an inhibitor, and the anti-factor VIII quantitates how high it is in Bethesda units. Given that the hematomas occurred while on treatment, it is unlikely that increasing the dose will improve the hematomas. Ice is a good approach, but determining whether the inhibitor is present is the most pressing need because, if present, a bypass agent may be needed, that is, recombinant factor VIIa (rFVIIa) or prothrombin complex concentrate (PCC).

2. A 26-year-old woman who is 20 weeks pregnant is referred for management recommendations at delivery. She has had menorrhagia in the past and oozing with dental extractions. A maternal uncle has hemarthroses. What is the most appropriate next step in the evaluation of this patient?

- A. Screen for von Willebrand disease.
- B. Screen for hemophilia carrier status and von Willebrand disease.
- C. Screening is not helpful because von Willebrand factor (VWF) and factor VIII increase during pregnancy.
- D. Obtain VWF and factor VIII in the 8th month of pregnancy.
- E. Plan DDAVP (desmopressin) for delivery and neuranesthesia.

Answer: D This woman may have a congenital bleeding disorder, with both a personal and a family bleeding history. Menorrhagia is a common symptom of von Willebrand disease, but it could also indicate hemophilia A or B carrier status. The history of a hemarthrosis (bleeding in a joint) in her uncle suggests he may have the X-linked congenital bleeding disorder, hemophilia, either A or B, and if inherited, gives her a 50-50 chance of being a carrier. Hemarthrosis is uncommon in other bleeding disorders but may occur in severe type 3 von Willebrand disease. Testing for von Willebrand disease or hemophilia carrier status is complicated by the well-known increase in VWF and factor VIII (but not factor IX) during pregnancy, potentially masking diagnosis of VWD or hemophilia carrier, but it is critical to screen VWF, factor VIII, and factor IX at the 8th month of pregnancy to plan for peripartum and neuranesthesia management. DDAVP is contraindicated at delivery because of major fluid loss and intravenous replacement, which could precipitate hyponatremia and seizures; VWF concentrate is the drug of choice for VWD, and recombinant factor VIII or IX is indicated for symptomatic factor VIII (or IX) for carriers.

3. A 47-year-old woman weighing 150 kg with factor VII deficiency is planning to undergo gastric bypass surgery. She is referred to you for hemostatic management of her surgery. What is the most appropriate management for her surgery?

- A. Fresh-frozen plasma (FFP) 15-20 U/kg before and for up to 1-2 days postoperatively
- B. PCC 50 IU/kg before and every 6 hours for 2 days postoperatively
- C. PCC 25 IU/kg before and every 6 hours for 2 days postoperatively
- D. Recombinant VIIa 90 µg/kg before and every 3-4 hours for 2 days postoperatively
- E. Recombinant VIIa 15 µg/kg before and on day 1 and 2 postoperatively

Answer: E The current treatment for congenital factor VII deficiency is low-dose factor VIIa: for surgery, it is given preoperatively and for several days postoperatively. After the tissue factor VIIa-triggered extrinsic coagulation pathway is activated, several days of treatment are usually sufficient to maintain the clot. Because obesity and surgery are both associated with risk for thromboembolism, the patient should be mobilized early in the postoperative course. FFP and PCC are alternative treatments, but levels of VII are low in FFP and in three-factor PCC, and the latter may increase thrombosis risk. rFVIIa in this patient would be less likely to increase thrombosis risk, given the patient's congenital deficiency (associated with lack of thrombin burst).

4. A 17-year-old high school senior with congenital factor XI deficiency is referred for management of his upcoming wisdom teeth extraction. His family history is negative for bleeding, and the patient has no bleeding history but has not had surgery. What is the most appropriate surgical management for this patient?

- A. FFP 15-20 U/kg preoperatively
- B. Amicar 50 mg/kg PO every 6 hours preoperatively
- C. DDAVP 0.3 µg/kg IV over 30 minutes preoperatively, and days 1 and 2 postoperatively
- D. Stimate 300 µg by nasal spray, given as 150 µg in each nostril preoperatively
- E. No preoperative treatment, but FFP 14-20 U/kg for postoperative bleeding

Answer: E At least half of those with factor XI deficiency have no personal or family history of bleeding, even with factor XI levels below 1%. Bleeding tendency is consistent within families. In the absence of family history, no treatment is given preoperatively, but if postoperative bleeding occurs, FFP is recommended. In Europe, a factor XI concentrate is available, but it not approved in the United States. Although Amicar, DDAVP, and Stimate may provide hemostasis, they are not specific for factor XI deficiency. For mucosal bleeding postoperatively, Amicar is a reasonable alternative.

5. A 50-year-old man with the lupus anticoagulant test (LAC) and positive β2-glycoprotein I (β2-GPI) antibody, as well as a recent lower extremity deep vein thrombosis, comes for a second opinion regarding need for long-term anticoagulation. In 2 weeks, he will complete a 6-month course of Coumadin 7.5 mg alternating with 5 mg to maintain an international normalized ratio (INR) of 2 to 3. What is the optimal management of this patient?

- A. Coumadin to maintain INR of 2.0 to 3.0 as long as benefits outweigh risks
- B. Coumadin to maintain INR of 2.0 to 3.0 plus low-dose acetylsalicylic acid (ASA; 81 mg) as long as benefits outweigh risks
- C. Coumadin to maintain INR of >3.0 as long as benefits outweigh risks
- D. Coumadin to maintain INR of >3.0 plus low-dose ASA (81 mg) as long as benefits outweigh risks.
- E. Stop Coumadin after 6 months, with careful monitoring for venous thromboembolism (VTE) recurrence.

Answer: A The occurrence of β2-GPI antibody and LAC with deep vein thrombosis is consistent with the antiphospholipid syndrome (APS). Individuals with APS are at increased risk for recurrent VTE, and thus anticoagulation should be continued as long as the benefits of anticoagulation outweigh bleeding risk. Several studies have demonstrated that standard Coumadin to an INR of 2.0 to 3.0 is adequate VTE prophylaxis for individuals with APS, with no added benefit to maintain INR above 3 for patients with antiphospholipid syndrome. ASA, other than in the setting of pregnancy, appears to provide no added benefit in clot protection in individuals with APS.

1. Which of the following statements is correct regarding disseminated intravascular coagulation (DIC)?
- A. There is always an underlying cause for DIC.
 - B. Laboratory screening test results showing normal to increased platelet counts or normal to shortened (not prolonged) prothrombin time (PT) and activated partial thromboplastin time (aPTT) essentially rule out DIC.
 - C. The primary pathophysiologic mechanism of DIC is bleeding; thrombosis can sometimes occur as a secondary event.
 - D. Large numbers of schistocytes (fragmented red cells) are characteristic blood smear findings in DIC.
 - E. The prolongation of PT and aPTT in DIC is a function of depletion of coagulation factors.

Answer: A DIC is a syndrome with many possible causes and never occurs in isolation as a primary event without an underlying cause. The results of laboratory screening tests of DIC (PT, aPTT, platelet count, D-dimers) can be highly variable; in fact, in chronic forms of so-called overcompensated DIC, most commonly due to malignant disease, the PT and aPTT can be actually shortened and the platelet count can even be elevated. The primary pathophysiologic mechanism of DIC, regardless of cause, is activation of the coagulation cascade leading to increased fibrin generation and microvascular fibrin deposition; therefore, DIC is a primarily thrombotic process. The systemic bleeding that is more often seen in acute DIC is due to a combination of depleted ("consumed") coagulation factors and platelets as well as the circulating anticoagulant effect generated by increased levels of D-dimers. Schistocytes (fragmented red cells) are nowhere nearly as prominent in the peripheral smear of a patient with DIC as they are in thrombotic thrombocytopenic purpura. As noted before, the prolongation of PT and aPTT in DIC is caused not just by the depletion of clotting factors ("consumption") but also by the powerful circulating anticoagulant effects of fibrin(ogen) degradation products.

2. Which of the following statements is correct regarding the coagulopathy of liver failure?
- A. In considering anticoagulation in a patient with liver failure, it should be taken into account that the already prolonged PT (and sometimes also aPTT) intrinsic to liver failure has already made the patient at least partially "auto-anticoagulated."
 - B. The degree of decrease in serum albumin is a better prognostic marker than the PT (or international normalized ratio [INR]) in a patient with acute viral hepatitis who has fulminant liver failure.
 - C. Patients with the coagulopathy of liver failure (prolonged PT and sometimes aPTT, with thrombocytopenia) have a serious bleeding risk but not thromboembolic risk.
 - D. In general, liver biopsy can be safely performed in a patient with liver failure when the PT and aPTT do not exceed 1.5 times control values and the platelet count is above 50,000.
 - E. In case of bleeding in a liver failure patient, prothrombin complex concentrates and recombinant human activated factor VII (rFVIIa) are first-line hemostatic agents.

Answer: D The American Association for the Study of Liver Diseases has stated that the bleeding risk-benefit ratio of liver biopsy must be carefully considered on a case-by-case basis. Nevertheless, most experts think that in general, biopsy can be performed without excessive risk of bleeding with the PT and aPTT both being less than 1.5 times control and the platelet count above 50,000. The notion that a patient in liver failure who already has a prolonged PT and thrombocytopenia is auto-anticoagulated is misleading. It ignores the complex pathophysiologic process of the coagulopathy of liver failure, which also involves important prothrombotic abnormalities. Patients with liver failure have a two-fold increase in the risk of venous thromboembolism compared with control individuals, even when the PT (INR) is prolonged. Prothrombin complex concentrates and rFVIIa are effective "general" hemostatic agents but carry a risk of thrombosis, especially in liver failure patients, who may have an impaired ability to clear those activated clotting factors. A prolonged PT is a useful prognostic indicator in various forms of liver disease and is actually a better index of prognosis than the serum albumin in acute viral hepatitis.

3. A 62-year-old man with known cirrhosis with portal hypertension and splenomegaly as well as alcoholic cardiomyopathy with poorly controlled heart failure is admitted to the intensive care unit with septic shock secondary to gram-negative sepsis. He is still intubated on hospital day 6. A hematology consultation is requested now because it is noted that his INR (PT) has been progressively rising since admission, from a baseline of 1.2 to 1.9. Which of the following is *not* likely to be contributing to this patient's rising INR?

- A. Cirrhosis
- B. Splenomegaly with hypersplenism
- C. Sepsis
- D. Heart failure
- E. Vitamin K deficiency

Answer: B Worsening liver function could be contributing to the rising INR in this setting but not the associated portal hypertension, splenomegaly, and hypersplenism. Sepsis could be causing DIC, and worsening right-sided heart failure could be causing passive hepatic congestion, both of which might be likewise contributing. The two major sources of vitamin K are its dietary intake and its synthesis by bacterial flora in the intestine. Both of these sources of vitamin K have been essentially eliminated in this patient because he has not been eating and his gut flora has been largely sterilized with the use of broad-spectrum antibiotics for sepsis; this is a prototypical setting for vitamin K deficiency. (Elimination of only one source of vitamin K, that is, poor nutrition or use of antibiotics, is usually not sufficient to cause clinically significant vitamin K deficiency.)

4. Which of the following is *not* a coagulation abnormality in advanced liver disease?

- A. Dysfibrinogenemia
- B. Disseminated intravascular coagulation
- C. Acquired factor VIII inhibitor
- D. Increased fibrinolytic activity
- E. Decreased synthesis of coagulation factors

Answer: C The pathophysiologic mechanism of bleeding in liver failure is complex and multifactorial. Impaired liver function reduces the synthesis of all coagulation factors because that organ is the major site of their synthesis. Because the liver is also the major site of clearance of trace amounts of circulating activated clotting factors, liver failure is associated with increased levels of these, leading to essentially a state of DIC. (It is why it is so difficult and sometimes impossible to distinguish the coagulopathy of liver failure from the coagulopathy of DIC; they may in fact often coexist in liver failure.) Enhanced fibrinolytic activity, partly secondary to DIC, is part of the picture in liver disease, as is the development of dysfibrinogenemia (functional abnormality of fibrinogen).

1. A 45-year-old man was diagnosed 3 days ago to have a left lower extremity deep venous thrombosis (DVT) by ultrasound. No provoking factors were identified. He was discharged from the emergency department without further work-up but with instructions to begin subcutaneous injections of therapeutic doses of a low-molecular-weight heparin together with daily warfarin at a dose of 7.5 mg/day, to be followed up by you in your primary care office. Which of the following would you do on this visit?
- A. Initiate imaging work-up for diagnosis of occult malignant disease.
 - B. Obtain a prothrombin time (international normalized ratio).
 - C. Repeat the lower extremity ultrasound.
 - D. Obtain pulmonary embolism protocol chest computed tomography.
 - E. Test for most common primary hypercoagulable states (thrombophilias).

Answer: B The emergency department physicians correctly initiated therapeutic heparin while at the same time beginning longer term warfarin oral anticoagulation to prevent recurrent venous thromboembolism (VTE). It is now time to begin regulating the warfarin dose on the basis of the prothrombin time, with a target international normalized ratio of 2.0 to 3.0. Although several studies have shown some increased risk of otherwise healthy individuals with VTE harboring an occult malignant neoplasm, a thorough history and physical examination, including stool samples for occult blood and basic studies like chest radiography and mammography in women, are considered to be sufficient. Advanced imaging studies to look for cancer are indicated only if abnormalities are found in this basic work-up. Another lower extremity ultrasound examination at this point is not indicated unless there is some uncertainty about the original diagnosis. The finding of a simultaneous, silent pulmonary embolism will not make any difference in your diagnostic and therapeutic plan. In fact, a large percentage (up to 50%) of patients with symptomatic lower extremity DVT would be found to have silent pulmonary emboli on imaging. Whatever might be found on blood tests for a primary hypercoagulable state at this point would not alter therapy, and the test results may be misleading right after an acute thrombotic event.

2. You are the primary care physician of a 50-year-old woman with a history of pregnancy-associated DVT 20 years ago. She has had no work-up for hypercoagulable states (thrombophilias). The patient has had no recurrent VTE and is not taking anticoagulants, but she is planning a nonstop flight from New York to Hong Kong. Which of the following would you recommend?
- A. Start aspirin 325 mg daily until return from Hong Kong.
 - B. Prescribe a single dose of subcutaneous injection of low-molecular-weight heparin immediately before embarking on flights to and from Hong Kong.
 - C. Recommend nothing except frequent ambulation and hydration on flights.
 - D. Do thrombophilia testing before flights.
 - E. Strongly recommend interrupting flights with layovers.

Answer: C A single episode of DVT in the past that was clearly related to a provoking event (i.e., pregnancy) does not require any special preventive measures before a long-haul flight in addition to the recommendation for ample hydration (with nonalcoholic beverages), frequent ambulation, and leg exercises. There is no evidence that prophylactic aspirin or low-molecular-weight heparin coverage for the flights would significantly reduce risk of flight-related VTE, even if a thrombophilia is found on testing in this situation. There is a very rough relationship between duration of long-haul air travel and risk of VTE, but the risk in any case is very small, and there is no evidence to suggest that it requires interruption of nonstop flights.

3. Which of the following statements is incorrect with regard to cancer-associated venous thromboembolism (VTE)?

- A. VTE may precede detection of an occult malignant neoplasm by months or years.
- B. Risk of cancer-associated VTE is further increased by surgery.
- C. Risk of cancer-associated VTE is further increased by some chemotherapies.
- D. VTE risk is increased with localized as well as with advanced metastatic cancers.
- E. Risk of recurrent VTE is best prevented by use of warfarin for as long as the cancer is active.

Answer: E Although prophylactic anticoagulation is recommended in most cancer patients after one or more thrombotic events, low-molecular-weight heparin has been demonstrated to be superior to warfarin in this particular setting. VTE may be an indicator of an occult malignant neoplasm months or even years before its discovery (see algorithm in Figure 176-4). Major surgery clearly increases the risk of thrombosis in a patient with cancer. The same is true for certain antineoplastic agents, including antiangiogenic agents (thalidomide, lenalidomide, bevacizumab, sunitinib, sorafenib), all-*trans*-retinoic acid and arsenic trioxide (used for treatment of acute promyelocytic leukemia), l-asparaginase, cisplatin, and methotrexate. Thrombotic complications are more frequent in cancer patients with advanced disease but can certainly also develop in those with localized tumors.

Ch / 177 TRANSFUSION MEDICINE

1. A 65-year-old, generally healthy man is transfused with 2 units of packed red cells in the recovery room after uncomplicated hip replacement surgery. Two hours later, he complains of acute onset of shortness of breath, and he is found to be hypertensive, cyanotic, and hypoxic. He is afebrile. Blood counts are normal. Chest radiograph shows bilateral opacities. A bedside echocardiogram is normal, as is the serum brain natriuretic peptide level. He is quickly transferred to the intensive care unit for imminent intubation and ventilatory support. Which of the following is the most likely diagnosis?

- A. Transfusion-associated graft-versus-host disease
- B. Bacterial contamination of the blood products
- C. Delayed transfusion reaction
- D. Transfusion-associated circulatory overload (TACO)
- E. Transfusion-related acute lung injury (TRALI)

Answer: E TRALI is now the leading cause of transfusion-related mortality. It typically presents as this case, with the patient becoming acutely symptomatic after having been transfused with any blood product within the previous 3 to 6 hours. Transfusion-associated graft-versus-host disease results from the transfusion of immunologically competent lymphocytes into an immunocompromised host, which this patient is not, and leads mainly to pancytopenia. A delayed transfusion reaction occurs much later, usually 3 to 7 days after the transfusion, and leads to hemolysis of red cells in the recipient by antibody produced as a result of the immune response to the transfusion. TACO can be difficult to distinguish from TRALI, but in this case, the normal echocardiogram and serum brain natriuretic peptide would argue against that (though not rule it out). Finally, septic transfusions are typically accompanied by hypotension and fever, which this patient did not have. Bacterial contamination of blood products occurs much more frequently with the transfusion of platelets, which are stored at room temperature: this patient received packed red cells. Very importantly, however, septic transfusions can mimic or even coexist with TRALI and, whenever there is any doubt, should be aggressively diagnosed and treated as such. The management of TRALI by itself is largely supportive.

2. Each of the following patients needs transfusion of 2 units of pack red cells for various reasons. Which one of them requires cytomegalovirus (CMV)-negative blood?
- A. 30-year-old woman in the third trimester of an uncomplicated pregnancy
 - B. 50-year-old man in remission from acute myelogenous leukemia
 - C. 87-year-old woman hospitalized for exacerbation of chronic heart failure
 - D. 45-year-old woman with systemic lupus erythematosus, maintained on prednisone
 - E. 55-year-old man, homeless and alcoholic, admitted with upper gastrointestinal bleed

Answer: A Blood product recipients who are CMV naïve (anti-CMV antibody negative) and have profoundly impaired immune systems are at increased risk for primary CMV infection when they receive CMV-positive blood products. CMV-negative blood products are required for pregnant mothers to prevent congenital CMV infection in the fetus. Profoundly immunocompromised individuals would include those receiving allogeneic or peripheral stem cell transplantations and untreated AIDS patients. In general, most institutions do not screen for CMV-negative blood products for patients needing transfusion who are receiving steroids or chemotherapy. Other indications in recipients for having CMV-seronegative blood transfused are intrauterine transfusion and neonates less than 37 weeks' gestation. Prestorage leukocyte depletion of blood products (red cells, platelets) significantly reduces the infection risk, but even for those products, most blood banks will still do CMV testing. (See Preventing Transmission of Cytomegalovirus.)

3. Which of the following statements regarding delayed transfusion reactions is correct?
- A. Delayed hemolytic transfusion reactions typically occur 48 to 72 hours after transfusion of the implicated unit.
 - B. Delayed transfusion reactions mostly occur in patients who have very low titers of preexisting antibodies from previous transfusions or through pregnancy and therefore had a negative antibody screen before transfusion; they are thus anamnestic responses.
 - C. Most patients present with fevers, chills, and back and flank pain.
 - D. Steroids should be avoided in the management of delayed transfusion reactions.
 - E. The hemolysis of delayed transfusion reactions is mostly intravascular.

Answer: B Delayed hemolytic transfusions (1) characteristically occur 3 to 7 days after transfusion of the implicated unit; (2) typically present without symptoms, with just a more rapid decline than usual in the recipient's hemoglobin (or failure to increase the hemoglobin after transfusion) accompanied by hemolytic chemistries including hyperbilirubinemia; and (3) should be treated with prednisone (1 to 2 mg/kg/day) in more severe reactions. The hemolysis in delayed transfusion reactions is mostly extravascular and results from an anamnestic response in recipients previously exposed to the antigen(s) through blood transfusions or pregnancy but having sufficiently low baseline titers of antibody to escape detection by routine screening. (See Delayed Reactions.)

1. The distinctive characteristic(s) of allogeneic hematopoietic stem cell transplantation include(s):

- A. The stem cell graft is free of contamination by malignant cells
- B. Associated with decreased complications compared with autologous and syngeneic hematopoietic stem cell transplantation
- C. Contains lymphocytes that are capable of mediating an immunologic reaction against foreign antigens
- D. Both A and C
- E. A, B, and C

Answer: D Both allogeneic and syngeneic grafts are free of tumor cell contamination. Allogeneic hematopoietic stem cell transplantation (HSCT) is associated with higher rates of treatment-related morbidity and mortality because of the potential for the development of graft-versus-host disease and need for immunosuppressive agents leading to higher risks of infection. Allogeneic transplantation contains lymphocytes that can mediate immunologic reactions against foreign antigens, including those on tumors leading to lower rates of relapse compared with either autologous or allogeneic HSCT.

2. The cells that contribute most to the graft-versus-tumor effects observed with allogeneic stem cell transplantation are

- A. neutrophils.
- B. monocytes.
- C. dendritic cells.
- D. T lymphocytes.
- E. B lymphocytes.

Answer: D Although neutrophils and monocytes play important roles in eliminating infections, they contribute little to observed graft-versus-tumor effect. B lymphocytes and dendritic cells have been demonstrated to play roles in the graft-versus-tumor effects observed with allogeneic hematopoietic stem cell transplantation ; however, T lymphocytes play the most important role. This has been most clearly evident clinically by the observation that infusion of donor T lymphocytes (i.e., donor lymphocyte infusion) after recurrence of cancer following allogeneic stem cell transplantation can alone result in sustained complete remissions.

3. All of the following are disadvantages for the clinical use of cord blood hematopoietic stem cells (HSCs) except

- A. clinical outcomes are in general inferior to fully HLA-matched sibling and volunteer unrelated donors.
- B. because of the unique immature biology of lymphocytes in umbilical cord blood, these transplants are associated with more GVHD.
- C. because of the small volume (50-150 mL) of cord blood, only a limited number of HSCs can be collected, which often prohibits their use in adults because successful engraftment correlates with the number of HSCs per patient body weight.
- D. cord blood HSCs are associated with delayed times to engraftment and immune reconstitution, leading to an increased rate of infection.
- E. after a cord blood unit is used, there is no possibility to obtain additional cells in the event of graft failure or if a donor lymphocyte infusion is required.

Answer: B Cord blood transplantation is generally associated with less graft-versus-host disease even when the donor and recipient are human leukocyte antigen (HLA) disparate. This is the major advantage of cord blood stem cells and permits the application of hematopoietic stem cell transplantation to a broader group of patients. Outcomes, however, are generally not as good as those observed with either fully HLA-matched sibling or volunteer donors in similar patients. The

limited number of HSCs, delayed hematopoietic recovery and immune reconstitution, and availability of only a single unit for each patient are major clinical disadvantages.

4. Risk factors for the development of acute graft-versus-host disease (GVHD) include all except which of the following?

- A. HLA mismatch
- B. Cytomegalovirus seronegativity of the donor or patient
- C. More advanced age in the patient and the donor
- D. Female donor (particularly a multiparous donor)
- E. Use of an unrelated donor

Answer: B Seropositivity, not negativity, in either the recipient or the donor is associated with a greater risk of developing acute GVHD. All of the other factors have also been associated with higher risks of developing acute GVHD. When a patient has more than one potential human leukocyte antigen-matched donors, these factors are used in the donor selection.

5. All of the following are considered standard indications for hematopoietic stem cell transplantation (HSCT) except

- A. allogeneic HSCT from HLA-matched donors for patients with intermediate- and high-risk acute myeloid leukemia in first remission.
- B. high-dose chemotherapy and autologous HSCT for patients with primary refractory and relapsed diffuse large B-cell lymphoma that remains chemotherapy sensitive.
- C. allogeneic HSCT from HLA-matched sibling in adult patients with advanced sickle cell disease.
- D. high-dose chemotherapy and autologous HSCT for patients with newly diagnosed multiple myeloma after induction therapy.
- E. allogeneic HSCT for patients with therapy-related acute myeloid leukemia.

Answer: C In all of the other clinical scenarios, either allogeneic or autologous HSCT has been demonstrated to significantly improve progression-free or overall survival. Several meta-analyses have demonstrated the benefit of allogeneic HSCT from human leukocyte antigen-matched donors for patients with intermediate- and high-risk acute myeloid leukemia in first remission. The benefit in patients with normal cytogenetics is being further delineated by molecular studies (e.g., FLT3-ITD). In relapsed, chemotherapy-sensitive diffuse large B-cell lymphoma, autologous HSCT has been demonstrated to result in improved progression-free and overall survival in randomized trials compared with conventional therapy. Although the continuing introduction of novel agents is changing clinical practice, autologous transplantation remains a standard component in the initial management of multiple myeloma patients. In the case of therapy-related acute myeloid leukemia, allogeneic stem cell transplantation is the only option that can provide long-term survival and possibly cure. Although there have been promising results with allogeneic HSCT in adults with advanced sickle cell disease, it still is considered investigational because ongoing trials attempt to identify the most appropriate patients in which to use this treatment.

1. A 65-year-old man reports symptoms of fatigue and loss of appetite. Physical examination demonstrates jaundice and an abdominal mass. CT scan of the abdomen reveals a mass at the head of the pancreas, with surrounding nodal involvement. The most appropriate next step in this patient's care is:

- A. Examination of serum biomarker studies including CEA and α -fetoprotein
- B. Image-guided biopsy of the abdominal mass
- C. Initiation of combination chemotherapy for advanced pancreatic cancer
- D. Referral for surgical resection and subsequent pathologic staging

Answer: B The diagnosis of locally advanced pancreatic cancer can often be made by CT-guided biopsy. In this patient with regionally advanced disease, surgery is unlikely to be beneficial; neither are serum biomarkers of use in making a tissue diagnosis, which is the first step in planning further treatment.

2. An 82-year-old woman is found to have a stage III left-sided invasive ductal carcinoma of the breast. She has well-controlled inflammatory bowel disease and adult-onset diabetes, lives alone, and has no immediate family. The most important factor in choosing a program for further diagnostic evaluation and treatment is her:

- A. Age
- B. Comorbid illnesses
- C. ECOG performance score
- D. Lack of family support

Answer: C A patient's performance status on the ECOG scale has been demonstrated to correlate well with tolerance of treatment and long-term outcome across a wide variety of malignancies to a much greater degree than age or individual comorbid illnesses.

3. In choosing a therapeutic regimen for systemic administration, of the following, which is the most important consideration for an adult cancer patient?

- A. Drug pharmacokinetics
- B. The ratio of the amount of treatment that can be delivered to the toxicity expected at that dose
- C. Route of drug administration
- D. The range of potential toxicities that might accompany drug administration

Answer: B Pharmacokinetic profiles and routes of administration are important factors in early drug development; however, the "therapeutic index" relating efficacy to toxicity is of paramount consideration in deciding which treatment should be employed.

4. Altered hepatic function would require substantive dose reduction of which one of the following anticancer agents?

- A. 5-Fluorouracil
- B. Imatinib
- C. Oxaliplatin
- D. Carboplatin

Answer: B Only imatinib, which unlike the other three drugs is metabolized by the hepatic cytochrome P-450 system, requires significant dose reduction for liver dysfunction.

5. A 52-year-old man with chronic hepatitis C develops a multifocal hepatocellular carcinoma, accompanied by malignant ascites and thrombocytopenia. The most appropriate approach to the control of the patient's malignant effusion is:

- A. Fluid restriction and diuresis
- B. Regular large-volume paracentesis in the clinic
- C. Cryosurgery for the major hepatic lesions
- D. Insertion of a permanent catheter for self-drainage

Answer: D This patient's tumor is not curable surgically; fluid restriction will lead to hyponatremia without producing symptomatic benefit; and large-volume paracentesis without ultrasound guidance in this patient carries an excessive risk of bleeding.

Ch / 180 **EPIDEMIOLOGY OF CANCER**

1. Which of the following types of cancer is not related to smoking?

- A. Bladder
- B. Esophagus
- C. Pancreas
- D. Acute lymphocytic leukemia
- E. Head and neck

Answer: D Acute lymphocytic leukemia is primarily a disease of children, and even in adults, it appears to be unrelated to smoking.

2. Excessive alcohol intake is associated with which one of the following malignancies?

- A. Laryngeal cancer
- B. Soft tissue sarcoma
- C. Neuroblastoma
- D. Melanoma
- E. Basal cell skin cancer

Answer: A Cancers of the head and neck, aerodigestive tract, and liver are well known to be associated with excessive alcohol consumption; no such association exists for pediatric malignancies or melanoma or for non-melanoma skin cancers. (See section on "Alcohol" under "Causes of Cancer.")

3. Which of the following malignancies is not associated with exposure to an infectious agent?

- A. Cervical cancer
- B. Hepatocellular cancer
- C. Head and neck cancer
- D. Chronic lymphocytic leukemia
- E. Gastric cancer

Answer: D Cervical and head and neck cancers are associated with the human papillomavirus, and hepatocellular cancer with chronic hepatitis B and/or C infection. Gastric cancer is associated with *Helicobacter pylori* infection. Chronic lymphocytic leukemia is not associated with exposure to an infectious agent. (See section on "Infections" under "Causes of Cancer.")

4. "Overdiagnosis" in the context of cancer screening efforts can be defined as:

- A. The excessive use of noninvasive imaging tests for asymptomatic patients
- B. The detection and treatment of lesions that might never have come to clinical attention
- C. The use of clinical algorithms for cancer diagnosis that have not been validated
- D. Use of plasma biomarkers of cancer to justify initiation of systemic treatment

Answer: B Treating tumors that are of no clinical significance (e.g., asymptomatic prostate cancers in men > 80 years of age) can produce morbidity with no therapeutic benefit.

5. The factor that is not related to cancer incidence is:

- A. age
- B. physical inactivity
- C. diet
- D. exposure to cold weather

Answer: D Although excessive sun (and concomitant UV) exposure is a well-known risk for the development of melanoma, no such relationship exists for exposure to colder climates. The rates of most cancers increase with age, often in a nonlinear (exponential) fashion. Physical inactivity is indirectly (if not directly) linked to cancer causation by its association with obesity. A large fraction of cancer incidence is acknowledged to be associated with dietary factors, although a definitive understanding of the mechanisms involved has been challenging. (See section on “Causes of Cancer.”)

Ch / 181 CANCER BIOLOGY AND GENETICS

1. A 36-year-old woman is found to have acute myelogenous leukemia. Family history obtained on diagnosis reveals that the patient’s mother died from a glioblastoma multiforme detected at the age of 40. The patient’s older brother died from recurrent osteogenic sarcoma at the age of 39, and her maternal grandmother succumbed to metastatic breast cancer before the onset of menopause. Mutations in which one of the following genes is associated with this familial cancer syndrome?

- A. *NF1*
- B. *APC*
- C. *TP53*
- D. *MLH1*
- E. *WT1*

Answer: C This family demonstrates the varied range of expression of the Li-Fraumeni syndrome, caused by mutations in the TP53 tumor suppressor. Although *NF1* mutations can be associated with breast cancer and leukemia, glioblastoma multiforme does not occur with this mutation. *MLH1* and *APC* mutations are associated with gastrointestinal malignancies for the most part. *WT1* mutations are specifically associated with familial Wilms tumor (See Table 181-1.)

2. Viral infections are not associated with which one of the following malignancies:

- A. Cervical cancer
- B. Merkel cell carcinoma
- C. B-cell non-Hodgkin’s lymphoma
- D. Colorectal carcinoma
- E. Hepatocellular carcinoma

Answer: D The major etiologic factor in the causation of cervical cancer is the human papillomavirus. Merkel cell carcinomas are associated with the Merkel cell polyomavirus. Epstein-Barr virus causes B-cell non-Hodgkin’s lymphoma, and hepatocellular carcinomas are associated with hepatitis B and C viruses. There is no virus known to be associated with the development of colon cancer.

3. One mechanism related to the unlimited replicative potential of tumor cells is:

- A. Low threshold for necrotic cell death
- B. Increased apoptotic gene expression
- C. Tumor cell heterogeneity
- D. Overexpression of telomerase
- E. Deregulation of cellular energetics

Answer: D High levels of tumor cell telomerase limit tumor cell senescence, promoting cellular longevity. Cells with a low threshold for necrosis or apoptosis have a diminished lifespan. Tumor cell heterogeneity is not directly related to the ability of tumor cells to replicate.

4. There is increasing evidence that specific genetic abnormalities in certain tumors are associated with alterations in tumor cell energy metabolism. Which of the following such associations is correct?

- A. Mutations in the mitochondrial fumarate hydratase gene and hereditary renal cancer
- B. Mutations in membrane-bound NADPH oxidase 1 and colon cancer
- C. Mutations in mitochondrial complex I and breast cancer
- D. Mutations in ribonucleotide reductase and CML

Answer: A Hereditary renal cancers have been associated with mutations in the fumarate hydratase gene that produce tumors that upregulate HIF-1 α and are highly vascular, related in part to enhanced oxidative glycolysis.

Ch / 182 MYELOYDYSPLASTIC SYNDROMES

1. A 69-year-old man presents with complaints of dyspnea on exertion, intermittent palpitations, and excessive fatigue. His history is significant only for gastroesophageal reflux and hypertension, and his medications include omeprazole and metoprolol. There is no family history of cancer or hematologic disorders. Physical examination reveals generalized pallor and regular tachycardia (106 beats/minute.)

A complete blood count is as follows:

White blood cell count: $6.1 \times 10^9/L$

51% neutrophils, 2% bands, 17% monocytes, 28% lymphocytes, 1% basophils, 1% eos

Hemoglobin 8.1 g/dL; mcv 92 fL

Platelets: $216 \times 10^9/L$

B12 and folate levels are within normal limits, and serum ferritin is 710 ng/ mL. The bone marrow is 70% cellular and exhibits erythroid dysplasia with <5% myeloblasts. Prussian blue reaction demonstrates 55% ring sideroblasts, consistent with a diagnosis of myelodysplastic syndrome, subtype refractory anemia with ring sideroblasts. The karyotype is normal male (46,XY). Which of the following genes is most likely to be mutated in this patient's marrow and blood cells?

- A. *BCR-ABL*
- B. *SF3B1*
- C. *GATA2*
- D. *TP53*
- E. *JAK2*

Answer: B This patient has refractory anemia with ring sideroblasts (RARS), according to the WHO classification of myelodysplastic syndromes (see Table 182-2). *SF3B1* mutations are strongly associated with RARS (occurring in 60-80% of cases; see Table 182-1). Mutations in the transcription factor *GATA2* are rare germline mutations in patients with familial MDS with monocytopenia; however, this patient has no family history of cancer or hematologic disorders. *TP53* mutation has a very poor prognosis and occurs in treatment-related MDS and is associated with a complex karyotype; however, this patient has not had such drug, toxic, or radiation exposures, and his karyotype is normal (46,XY). The *BCR-ABL* mutation is characteristic of Philadelphia chromosome-positive chronic myelogenous leukemia (CML); however, this patient does not have that clinical phenotype and does not have the Philadelphia chromosome on cytogenetics. *JAK2* mutations (specifically *JAK2-V617F*) are found in a large percentage of chronic myeloproliferative neoplasms, especially polycythemia vera, and can also be seen in RARS with thrombocytosis; however, the patient has a normal platelet count.

2. A 51-year-old elementary school teacher develops fatigue, dyspnea on exertion, and cold/tingling extremities. Exam reveals generalized pallor and mildly decreased proprioception and hyperreflexia. Past history is significant for hypertension, impaired glucose tolerance, and bariatric surgery 3 years ago for obesity. Her medications include metoprolol, aspirin, a multivitamin, and zinc and echinacea supplements.

The complete blood count is as follows: hemoglobin 10.2 g/dL, MCV 88 fL, white blood cell count $2.9 \times 10^9/L$, absolute neutrophil count 380/mm³, and platelet count $218 \times 10^9/L$. Peripheral blood smear shows some hypochromic red cells and neutropenia but is otherwise unrevealing.

Serum B12, red cell folate, serum ferritin, and homocysteine levels are within normal limits. A serum chemistry panel is unremarkable. The bone marrow is normocellular for age, with erythroid dysplasia, 40% ring sideroblasts, granulocytic dysplasia with vacuolization of neutrophil precursors, and no increase in myeloblasts. The karyotype is normal female. What is the most likely cause of her cytopenias?

- A. Congenital sideroblastic anemia
- B. Myelodysplastic syndrome, subtype refractory anemia with ring sideroblasts
- C. Vitamin/mineral deficiency
- D. Alcohol abuse
- E. Myeloproliferative neoplasm

Answer: C The differential diagnosis in this patient from among the choices offered is quite challenging. Vitamin and mineral deficiencies like advanced folate or B12 deficiency can cause dysplastic changes in blood cell precursors in the bone marrow that might be difficult to distinguish morphologically from MDS. In particular, copper deficiency is being increasingly recognized today as a cause of sideroblastic anemia (which this patient has, with 40% ring sideroblasts in the marrow) in individuals who have had bariatric surgery (as in this case). Copper deficiency also causes neuropathy, which appears to be present here. Therefore, the picture is most consistent with copper deficiency secondary to bariatric surgery. MDS (refractory anemia with ringed sideroblasts [RARS]) has many of the features present in this case, including dysplastic changes in both myeloid and erythroid precursors in the marrow, but only drawing a blood copper level and giving a therapeutic trial of copper replacement would rule out the working diagnosis. Congenital sideroblastic anemia can present in adulthood, but it is much less likely here because these inherited anemias typically have changes only in the erythroid series. There is nothing to support the diagnosis of alcohol abuse or a myeloproliferative neoplasm in this case presentation. (See: Steensma DP. Dysplasia has a differential diagnosis: distinguishing genuine myelodysplastic syndromes [MDS] from mimics, imitators, copycats and impostors. *Curr Hematol Malig Rep.* 2012;7:310-320.)

3. A 58-year-old woman is found to be anemic during an evaluation for excessive fatigue. Her history is significant only for cholecystectomy and quiescent rheumatoid arthritis. Other than generalized pallor and borderline regular tachycardia, her exam is unrevealing. A complete blood count is as follows:

Hemoglobin 6.0 g/dL

Mean cell volume 102 fL

White blood count $4.8 \times 10^9/L$

Absolute neutrophil count $2.55 \times 10^9/L$

Platelet count $466 \times 10^9/L$

The reticulocyte count is 0.7%. Serum chemistries and serum B12 and red blood cell folate levels are normal. A peripheral blood smear is nondiagnostic. The serum erythropoietin level is measured at 702 U/L.

The patient is admitted to the hospital, where red cell transfusions are administered. There is no evidence of gastrointestinal bleeding. Bone marrow aspirate/biopsy shows a hypercellular marrow with erythroid dysplasia. Megakaryocytes are increased in number, and many are dysplastic with occasional small monolobated forms. The karyotype is 46,XX del(5)(q13q33) [18]/46,XX [2]. Which of the following is the most appropriate initial treatment for this patient?

- A. Darbepoetin alfa
- B. Lenalidomide
- C. Azacitidine
- D. Antithymocyte globulin plus cyclosporine
- E. Referral for allogeneic stem cell transplantation

Answer: B This patient has the 5q- syndrome, which has a relatively favorable prognosis among the myelodysplastic syndromes. It was the first form of MDS found to be significantly responsive to lenalidomide therapy. Initial trials of lenalidomide in these patients demonstrated high response rates, including a nearly 70% transfusion independence rate and better than 30% cytogenetic normalization rate lasting a median of more than 2 years. (See section on “Immunomodulatory Agents” under “Disease-Modifying Therapy” in the Treatment box.) Therefore, lenalidomide should be first-line treatment for this patient.

4. A 79-year-old man with a history of congestive heart failure due to multivessel coronary artery disease (most recent echocardiogram showed a left ventricular ejection fraction of 30%), renal insufficiency due to hypertension, and two hospitalizations for exacerbations of chronic obstructive pulmonary disease within the last year has developed worse fatigue and dyspnea. His medications include furosemide, lisinopril, metoprolol, aspirin, inhaled salmeterol and fluticasone, and fluvastatin. A complete blood count is as follows:

Hemoglobin 8.8 g/dL

Mean cell volume 103 fL

White blood cell count $1.9 \times 10^9/L$

Absolute neutrophil count $0.48 \times 10^9/L$

Platelet count $77 \times 10^9/L$

Serum vitamin B12 and folate levels are within normal limits. The creatinine is 1.8 mg/dL, and blood urea nitrogen is 52; a chemistry group is otherwise unremarkable.

The bone marrow is hypercellular for age with multilineage dysplasia, increased reticulin fibrosis, and 12% blasts, and the marrow karyotype is complex with 4 different chromosome abnormalities and 2 separate clones. Which of the following is the most appropriate treatment for this patient?

- A. Induction chemotherapy with daunorubicin and cytarabine
- B. Lenalidomide
- C. Epoetin alfa
- D. Azacitidine
- E. Allogeneic stem cell transplantation

Answer: D Azacitidine. This patient has higher-risk MDS, associated with both increased blasts and a high-risk, complex karyotype. He is too old and has too many comorbid conditions to be a viable candidate for allogeneic stem cell transplantation or intensive induction chemotherapy. Azacitidine, a DNA methyltransferase inhibitor, has been demonstrated in a randomized trial to improve survival compared to conventional care (i.e., supportive care or low-dose cytarabine). Patients who have thrombocytopenia and lack chromosome 5q deletion are less likely to respond to lenalidomide.

5. A 19-year-old man was recently found to have pancytopenia (hemoglobin 9.3 g/dL, absolute neutrophil count of $0.45 \times 10^9/L$, and platelet count of $23 \times 10^9/L$) during routine follow-up of a pediatric cancer. At age 15, he was treated for locally advanced osteosarcoma of the left tibia, with limb sparing surgery, radiotherapy, and adjuvant combination chemotherapy. He sees his pediatric oncologist annually, and at his last visit 9 months ago there was no evidence of recurrence of the sarcoma. Other than fatigue, he is asymptomatic.

His bone marrow aspirate and core biopsy show trilineage dysplasia and 6% myeloblasts, consistent with a diagnosis of MDS, subtype refractory anemia with excess blasts-1. The karyotype is complex and includes 2 marker chromosomes and monosomy 7 in 16 of 20 examined metaphases. He has 3

siblings, and one is fully HLA matched. Which of the following treatments is most appropriate for this patient?

- A. Allogeneic stem cell transplantation
- B. Lenalidomide
- C. Azacitidine
- D. Decitabine
- E. Epoetin alfa and filgrastim

Answer: A Allogeneic stem cell transplantation. Unfortunately, this patient has developed a late complication of curative therapy for his sarcoma: secondary, therapy-related MDS (t-MDS). t-MDS has a poor prognosis and often progresses rapidly to AML. This patient would benefit from proceeding to allogeneic stem cell transplant as soon as possible, because this is the only potentially curative therapy for his MDS. Since he does not have >10% blasts, there is no clear role for pre-transplant cytoreductive therapy.

Ch / 183

THE ACUTE LEUKEMIAS

1. A 66-year-old man presents with fatigue and is found to have pancytopenia with a hematocrit of 31%, a white blood cell count of 2300/ μ L with peripheral blasts, and a platelet count of 9000/ μ L. A bone marrow study shows 60% myeloblasts consistent with M1 acute myelogenous leukemia (AML). The patient had previously been in outstanding health. The choice is made to attempt induction therapy with daunorubicin and cytarabine. Which of the following statements is correct concerning prophylaxis against bleeding during induction?

- A. No platelet prophylaxis is necessary. It is sufficient to wait until clinical evidence of bleeding (petechiae or ecchymoses) for transfusing platelets.
- B. Prophylactic platelet transfusions from random donors should be given when platelet counts drop below 10,000/ μ L.
- C. Prophylactic platelet transfusions from random donors should be given when platelet counts drop below 20,000/ μ L.
- D. Prophylactic platelet transfusions from HLA-matched donors should be given when platelet counts drop below 10,000/ μ L.
- E. Prophylactic platelet transfusions from HLA-matched donors should be given when platelet counts drop below 20,000/ μ L.

Answer: B See Stanworth SJ, Estcourt LJ, Powter G, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. *N Engl J Med*. 2013;368:1771-1780.

2. A 24-year-old woman presents with bleeding gums and easy bruising. She is found to have a hematocrit of 29%, a white blood cell count of 4800/ μ L with 5% peripheral promyelocytes, and a platelet count of 38,000/ μ L. A bone marrow study shows morphologic and molecular evidence of promyelocytic leukemia. She is begun on ATRA and daunorubicin. Infection prophylaxis includes a quinolone and Bactrim. Six days after starting therapy, the patient presents with fever and increasing shortness of breath that has developed over several days. Her white blood cell count has risen to 15,000/ μ L with 20% promyelocytes and metamyelocytes. A chest radiograph shows diffuse pulmonary infiltrates. What would be the most appropriate next step?

- A. Add daunorubicin to therapy.
- B. Add arsenic trioxide to therapy.
- C. Perform a bronchoscopy.
- D. Add posaconazole for antifungal coverage.
- E. Temporarily discontinue the ATRA and add dexamethasone.

Answer: E See Sanz MA, Lo-Coco F. Modern approaches to treating acute promyelocytic leukemia [review]. *J Clin Oncol*. 2011;29:495-503.

3. An 84-year-old man presents with increasing angina and is found to have a hematocrit of 21%, a white blood cell count of 22,000/ μ L, and a platelet count of 78,000/ μ L. A bone marrow examination shows AML with complex cytogenetics including monosomy 7. The patient has a known past history of coronary artery disease, hypertension, and peripheral vascular disease. His ECOG performance status is 2. Which of the following would you recommend?

- A. Supportive care only
- B. Supportive care plus therapy with low-dose cytarabine
- C. Imatinib
- D. Conventional induction with cytarabine and daunorubicin
- E. Conventional induction with cytarabine but with reduced-dose daunorubicin

Answer: B See Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol.* 2010;28:562-569.

4. A 44-year-old woman presents with increasing bone pain and pallor and is found to have a hematocrit of 24%, a white blood cell count of 32,000/ μ L with circulating myeloblasts, and a platelet count of 45,000/ μ L. A bone marrow study shows AML with t(4;11). Three years earlier, she had been diagnosed with breast cancer and had been treated with surgery, radiation, and adjuvant chemotherapy including cyclophosphamide and doxorubicin. She is treated for her AML with daunorubicin and cytarabine and after one cycle achieves a complete remission. She does not have a matched sibling or a matched unrelated donor. What would you recommend for her further therapy?

- A. Three cycles of consolidation therapy using high-dose cytarabine
- B. Three cycles of consolidation therapy using high-dose cytarabine combined with gemtuzumab ozogamicin
- C. Cord blood transplantation as soon as possible
- D. Autologous stem cell transplantation as soon as possible
- E. Three cycles of consolidation therapy followed by autologous transplantation

Answer: C See Lowenberg B, Pabst T, Vellenga E, et al. Cytarabine dose for acute myeloid leukemia. *N Engl J Med.* 2011;364:1027-1036.

5. A 74 year-old woman presents with increasing peripheral edema and is found to have a hematocrit of 26%, a white blood cell count of 38,000/ μ L with circulating lymphoblasts, and a platelet count of 110,000/ μ L. A bone marrow shows Ph+ acute lymphoblastic leukemia. She has a prior history of compensated congestive heart failure. What therapy would you recommend for her?

- A. Supportive care only
- B. Supportive care plus low-dose cytarabine
- C. Dasatinib plus dexamethasone
- D. Vincristine, prednisone, l-asparaginase, daunorubicin, and imatinib
- E. Gemtuzumab ozogamicin

Answer: C See Bassan R, Hoelzer D. Modern therapy of acute lymphoblastic leukemia [review]. *J Clin Oncol.* 2011;29:532-543.

1. 35-year-old man was diagnosed with chronic phase chronic myelogenous leukemia (CML) following a regular check-up. He had no significant comorbidities or medical history and was initiated on imatinib 400 mg daily. At 12 months, he achieved a complete cytogenetic response with transcripts level of 0.6% (IS). At 18 and 24 months, his transcripts levels were 0.5% and 0.4% (IS), respectively. Which of the following would be the next step in treatment?

- A. Continue imatinib.
- B. Switch to nilotinib.
- C. Switch to dasatinib.
- D. Switch to ponatinib
- E. Consider allogeneic stem cell transplantation

Answer: A "Resistance" to imatinib therapy requires a change of therapy to other tyrosine kinase inhibitors (TKIs), TKI combinations with chemotherapy, or consideration of allogeneic stem cell transplantation. Resistance can be defined as persistent 100% Ph positivity after 6 months of therapy, Ph positivity of more than 35% after 12 months of therapy, or cytogenetic or hematologic relapse. It is important to emphasize that many patients with CML resistance to a TKI therapy may be noncompliant with the treatment. This should be discussed clearly with patients when they exhibit signs of CML progression by either molecular or fluorescent in situ hybridization studies. If they are noncompliant, they may continue on the same TKI treatment with emphasis on compliance and evaluated 3 to 6 months later, before CML resistance is declared. Among patients in complete cytogenetic response on a particular TKI, failure to achieve a major molecular response in a patient with a complete cytogenetic response does not, at present, indicate imatinib resistance to the particular TKI or the need to change therapy. The rate of resistance to imatinib in chronic phase CML is less than 4% per year; for those who achieve a complete cytogenetic response, the rate of resistance beyond year 3 of imatinib therapy is 1% or less, suggesting the durable stability of a complete cytogenetic response on imatinib and the predictability of the CML course after such a response is obtained.

2. A 68-year-old woman was diagnosed with chronic phase CML after a regular check-up. She was initiated on dasatinib 100 mg daily. At 6 months, she achieved a major cytogenetic response with transcripts level of 9% (IS). At 12 months, she lost her cytogenetic response with transcripts levels of 30% (IS). A T315I mutation was identified. Which of the following would be the next step in treatment?

- A. Increase dasatinib dose to 140 mg daily.
- B. Switch to nilotinib.
- C. Switch to bosutinib.
- D. Switch to ponatinib.
- E. Switch to omacetaxine.

Answer: D Patients who develop resistance to first-line TKI in chronic phase are offered second-line or third-line TKI based on their mutation analysis. A T315I mutation in the CML clone requires therapy with ponatinib and (as of today) early consideration of allogeneic stem cell transplantation until the results of ponatinib therapy mature. Mutations involving V299L, T315A, or F317LIV/1/C are sensitive to nilotinib therapy. Mutations involving Y253H, E255K/V, or F359/V/C/I are sensitive to dasatinib and bosutinib therapy. Omacetaxine is approved for patients who had failed two TKIs.

3. A 34-year-old woman was diagnosed with chronic phase CML and was initiated on imatinib 400 mg daily. She achieved a complete cytogenetic response by 12 months of therapy. Her last transcripts level was reported to be 0.5% (IS). She comes to see you for advice regarding her desire to become pregnant. Which of the following would be the next step in treatment?

- A. Stay on imatinib and try to conceive.
- B. Switch to dasatinib and try to conceive.
- C. Switch to nilotinib and try to conceive.
- D. Switch to ponatinib and try to conceive.
- E. You should not conceive while you are taking any TKIs.

Answer: E CML during pregnancy may be controlled with pheresis in the first trimester and then with hydroxyurea until delivery. Use of interferon- α during pregnancy has been reported anecdotally to be safe. An analysis of 125 babies delivered to women with CML on imatinib therapy (who discontinued imatinib after the pregnancy was known) showed most babies to be healthy. However, the study showed imatinib therapy to be associated with syndrome of ocular, skeletal, and renal abnormalities in three babies delivered. Therefore, imatinib (and presumably other TKIs, although there is little experience with them) should be discontinued immediately when pregnancy is documented, but abortion is not recommended because fetal malformations are rare. Partners of men with CML on TKI therapy who become pregnant have delivered normal babies.

Ch / 185

NON-HODGKIN LYMPHOMAS

1. A 66-year old man develops cough and chest pain. A chest radiograph shows a mediastinal mass. A biopsy of the mass shows diffuse large B-cell lymphoma. Additional studies reveal enlarged lymph nodes in the para-aortic and mesenteric regions. His bone marrow biopsy is negative. His performance status is otherwise normal, and his serum lactate dehydrogenase level is normal. How should this man be treated?

- A. Observation (watch and wait)
- B. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
- C. CHOP + rituximab
- D. Radiation to the chest and abdomen
- E. CHOP + rituximab followed by autologous stem cell transplantation

Answer: C This man has a stage III diffuse large B-cell lymphoma. His IPI score is II (low-intermediate risk). A watch and wait approach is reasonable for some patients with indolent lymphoma, but not for patients with diffuse large B-cell lymphoma. There is no role for radiation, alone, in this situation. Treatment with CHOP would yield a high response rate, although randomized trials show improved survival with the addition of the anti-CD20 antibody rituximab (Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood*. 2010;116:2040-2045). There is no evidence that upfront autologous stem cell transplantation is beneficial for patients in low-risk groups.

2. A 27-year old woman has an unexplained 20-lb weight loss, drenching night sweats, and bulky bilateral cervical lymphadenopathy. A chest radiograph shows bilateral cervical lymphadenopathy. Fine-needle aspirate (FNA) of a cervical lymph node reveals cells consistent with a B-cell non-Hodgkin lymphoma. What should you do next?

- A. Perform FNA on another cervical lymph node.
- B. Prescribe antibiotics for 10 days and reevaluate.
- C. Start ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine).
- D. Perform an excision biopsy of a cervical lymph node.
- E. Start CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab.

Answer: D This woman has an obvious systemic illness. Empirical antibiotic therapy would be inappropriate. All non-Hodgkin lymphomas are treatable, and many are curable. It is essential to have an accurate diagnosis before starting therapy so that appropriate therapy is administered. Core needle biopsies can occasionally be used for a primary diagnosis if the specimen is handled properly. Fine-needle aspirates should not be used to diagnose lymphoma, and they preclude an accurate diagnosis of the specific subtype of non-Hodgkin lymphoma. In most cases, an excisional biopsy is necessary (and is always preferred) for the initial diagnosis. Her diagnosis from FNA is inadequate. An excisional biopsy with review by an expert hematopathologist is necessary for appropriate treatment (Swerdlow SH. Lymphoma classification and the tools of our trade: an introduction to the 2012 USCAP Long Course. *Mod Pathol.* 2013;26:S1-S14). It would be inappropriate to start CHOP + rituximab before an accurate diagnosis is established. The ABVD regimen is used for Hodgkin lymphoma.

3. Patients with mantle cell lymphoma are most likely to have the following cytogenetic abnormality in their lymph node biopsy?

- A. t(11;14)
- B. t(11;18)
- C. t(14;18)
- D. t(8;14)
- E. t(2;5)

Answer: A Non-Hodgkin lymphomas are often associated with cytogenetic abnormalities. These abnormalities often consist of translocations that result in overproduction of fusion proteins with result in cell proliferation or inhibit apoptosis (Nogai H, Dörken B, Lenz G. Pathogenesis of Non-Hodgkin lymphoma. *J Clin Oncol.* 2011;29:1803-1811). Certain subtypes of non-Hodgkin lymphoma are associated with specific cytogenetic abnormalities. The t(11;18) is associated with MALT lymphoma, the t(14;18) is associated with follicular lymphoma, the t(8;14) is associated with Burkitt's lymphoma, and the t(2;5) is associated with anaplastic large cell lymphoma. The t(11;14) is characteristic of mantle cell lymphoma. This translocation results in overproduction of cyclin D1 and resultant cell proliferation.

4. A 40-year old woman has a history of a mediastinal large B-cell lymphoma. She was treated several years ago with R-CHOP followed by radiation therapy involving the chest and neck. She comes to you with complaints of fatigue, trouble concentrating at work, and feeling cold. Her examination reveals no lymphadenopathy. Her chest radiograph is unchanged from 1 year ago. Laboratory tests are normal except for high cholesterol. What should you do?

- A. Order a computed tomography (CT) scan of the chest, abdomen, and pelvis.
- B. Check serum vitamin B12 and folic acid levels.
- C. Perform a bone marrow aspirate and biopsy.
- D. Check a thyroid-stimulating hormone (TSH) level.
- E. Order a positron emission tomography (PET) scan.

Answer: D It is important to monitor patients for late effects of therapy. Although disease recurrence should always be considered, there is no evidence of this. It would be inappropriate to order additional imaging at this time. There is no evidence that she is B12 or folic acid deficient. Hypothyroidism is a frequent complication of radiation therapy and should always be considered. Her history increases her risk for cardiovascular disease, and strict control of modifiable risk-factor, such as cholesterol, is necessary (http://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf).

5. Which patient is least likely to have a lymphoma associated with the Epstein-Barr virus (EBV)?

- A. A 42-year old man with a history of a liver transplantation
- B. A 31-year old woman with chronic HIV infection
- C. A 45-year old woman with an extranodal NK/T-cell lymphoma
- D. A 68-year old woman with follicular lymphoma
- E. A child from sub-Saharan Africa with Burkitt's lymphoma

Answer: D EBV, as well as other infectious agents, is associated with several types of non-Hodgkin lymphoma *Semin Diagn Pathol.* 2011;28:178-187). Follicular lymphoma is not usually associated with EBV. (De Falco G, Rogena EA, Leoncini L. Infectious agents and lymphoma.

Ch / 186 **HODGKIN LYMPHOMA**

1. A 23-year-old man has noticed bilateral lower neck firm masses eventually reaching about 3 cm in greatest diameter over the past 3 months, which have not resolved after 2 more weeks of observation during which he took a 7-day course of oral antibiotics. A fine-needle aspiration biopsy reveals predominantly small lymphocytes and granulocytes, small numbers of eosinophils, and occasional monoclonal large multinucleated cells that are positive for CD30 and variably positive for CD20 and are judged consistent with Hodgkin-Reed-Sternberg cells and a diagnosis of probable Hodgkin lymphoma. What is the most appropriate next step in this patient's evaluation?

- A. Computed tomography (CT) of the neck, chest, abdomen and pelvis
- B. Whole body positron emission tomography/computed tomography (PET/CT)
- C. Bone marrow biopsy
- D. Whole lymph node excisional biopsy of an abnormal neck lymph node
- E. A 14-day course of ciprofloxacin

Answer: D This patient probably has Hodgkin lymphoma; however, a firm diagnosis cannot be made based on needle aspiration biopsy. Other conditions that could be present and cannot be distinguished from Hodgkin lymphoma using only a needle aspiration biopsy include anaplastic large cell lymphoma, primary mediastinal B-cell lymphoma, T-cell-rich B-cell lymphoma, or unusual atypical lymphoid hyperplasia. Accurate diagnosis of Hodgkin lymphoma requires at least an incisional biopsy of involved nodal tissue, preferable an entire enlarged lymph node. Initiating extensive evaluation or further delay in assessment without a firm diagnosis is inappropriate.

2. A 26-year-old schoolteacher seeks a second opinion from you. She has been found to have neck and mediastinal nodular sclerosing Hodgkin lymphoma based on an excisional biopsy of a left supraclavicular fossa lymph node, PET/CT scanning showing definitely enlarged lymph nodes in the lower neck bilaterally, the mediastinum and closely contiguous left hilar lymph nodes with standardized uptake values (SUVs) ranging from 4.2 to 18.9, but no disease outside the neck and thorax. The largest nodal mass is 4.5 cm in diameter. Peripheral blood cell counts, serum creatinine, and screening liver function tests including alkaline phosphatase are all normal except for a mildly elevated neutrophil count. She has received a recommendation that she be treated with six cycles of ABVD chemotherapy (Adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine) followed by involved-field radiation if residual disease remains abnormal on PET/CT scanning. What is your recommendation?

- A. Omit the chemotherapy and proceed with irradiation to the neck, axillae. and mediastinum using the mantle technique.
- B. Shorten the ABVD chemotherapy to two cycles and follow that with mantle radiation.
- C. Shorten the ABVD chemotherapy to two cycles and follow that with involved-field radiation.
- D. Perform a PET/CT scan after two cycles of ABVD chemotherapy and stop treatment if it is negative.
- E. Agree with the previous specialist's recommendation.

Answer: C Treatment with two cycles of ABVD followed by involved-field radiation has been shown be equivalent to more chemotherapy plus involved-field radiation. Answer B is incorrect because it is not necessary to use a larger radiation field, and the larger field would be expected to increase the risk for serious late complications. Answer D is incorrect because it has not been proved that radiation can be omitted based on a negative PET/CT scan after only two cycles of chemotherapy. The previous consultant recommended more chemotherapy than is necessary for limited-stage Hodgkin lymphoma.

3. An 18-year-old college student is referred to you to investigate new palpable inguinal lymphadenopathy. He has been experiencing drenching night sweats on at least 4 nights each week for the past month and has lost 7 kg of weight on a baseline weight of 84 kg. You document palpable abnormal lymph nodes in the left neck, left axilla, and bilateral inguinal/ femoral areas. An excisional biopsy of a left supraclavicular fossa lymph node demonstrates nodular sclerosing Hodgkin lymphoma, and PET/CT scanning shows definite enlarged lymph nodes in the lower neck bilaterally, mediastinum, retroperitoneum, common iliac, and inguinal/femoral areas and there are multiple nodules within the spleen, with SUVs ranging from 3.2 to 28.9. The largest nodal mass is in the mediastinum and measures 15.5 cm in diameter. Peripheral blood cell counts show hemoglobin 9.2 g/L, white blood cell count $13.5 \times 10^9/L$, normal differential except for increased neutrophils, and normal serum creatinine. Alkaline phosphatase and lactate dehydrogenase are both twice the upper limit of normal. Bone marrow biopsy demonstrates involvement with Hodgkin lymphoma. What is your recommendation?

- A. Initiate ABVD chemotherapy with the plan to continue through six cycles if the lymphoma shows continuous response through that time.
- B. Give escalated BEACOPP chemotherapy (bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) for eight cycles followed involved-field radiation.
- C. Give four cycles of ABVD followed by high-dose chemotherapy and autologous peripheral blood stem cell transplantation.
- D. Give two cycles of ABVD followed by six cycles of escalated BEACOPP chemotherapy if the PET/CT scan remains abnormal after the ABVD.
- E. Give involved-field radiation followed by six cycles of ABVD.

Answer: A ABVD has emerged as the best chemotherapy overall because of its balance of high efficacy and moderate toxicity. Although escalated BEACOPP produces a higher initial response rate, overall survival is not improved compared with ABVD. Neither regimen must be followed by radiation if the chemotherapy induces a complete response as measured by PET/ CT scanning. Planned escalation to high-dose chemotherapy and autologous peripheral blood stem cell transplantation has not been shown to improve overall survival for Hodgkin lymphoma. Altering treatment based on interim PET/CT scanning, although an attractive concept, has not been shown to improve ultimate disease control for Hodgkin lymphoma. It is never appropriate to initiate treatment of Hodgkin lymphoma with radiation because that will compromise safe delivery of necessary chemotherapy without improving outcome.

4. Two years ago, you treated a 47-year-old housewife with six cycles of ABVD for stage IIIA mixed-cellularity Hodgkin lymphoma, and the patient has been off treatment and well for 18 months. She now returns with new palpable bilateral neck lymph nodes, and a biopsy confirms recurrent Hodgkin lymphoma. Complete reassessment confirms recurrent disease in the neck and retroperitoneum. What is your recommendation?

- A. Initiate MOPP/ABVD chemotherapy (mechlorethamine, vincristine, procarbazine, and prednisone alternating with ABVD) with the plan to continue through six cycles if the lymphoma shows continuous response through that time.
- B. Give escalated BEACOPP chemotherapy (bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) for six cycles.
- C. Give mantle followed by inverted-Y extended-field radiation.
- D. Give two cycles of ABVD followed by high-dose chemotherapy and autologous peripheral blood stem cell transplantation.
- E. Give two cycles of cisplatin- or carboplatin-based multiagent chemotherapy followed by high-dose chemotherapy and autologous peripheral blood stem cell transplantation.

Answer: E Choices A, B and D are incorrect because repeating ABVD chemotherapy by itself or with addition of other agents is inappropriate since this patient's lymphoma has already demonstrated resistance to ABVD by relapsing. Although wide-field radiation may be able to cure some patients with lymph node-only Hodgkin lymphoma relapsing after ABVD, it is much less likely to do so than high-dose chemotherapy and autologous peripheral blood stem cell transplantation and is likely to

contribute substantially to potentially lethal toxicity if treatment is necessary for another relapse. Two to three cycles of cisplatin- or carboplatin-based multiagent chemotherapy followed by high-dose chemotherapy and autologous peripheral blood stem cell transplantation is the treatment of choice for Hodgkin lymphoma that has relapsed after primary treatment with ABVD for advanced-stage disease.

5. Which of the following statements about Hodgkin lymphoma occurring in an individual known to harbor HIV infection is *true*?

- A. Coincident HIV infection can be ignored when found in a patient with Hodgkin lymphoma.
- B. HIV-associated Hodgkin lymphoma is incurable and thus best approached with palliative intent.
- C. Stage IV is uncommon in patients with HIV-associated Hodgkin lymphoma.
- D. Patients with HIV-associated Hodgkin lymphoma should be treated with standard ABVD.
- E. Patients with HIV-related Hodgkin lymphoma are at high risk for central nervous system (CNS) involvement with the lymphoma.

Answer: D Although patients with HIV-associated Hodgkin lymphoma can and should be treated curatively with standard chemotherapy, such as ABVD (B is *false*; D is *true*), these patients require substantial special supportive care with antiviral, antifungal, and anti-*Pneumocystis* antibiotics, coincident treatment with highly active antiretroviral therapy (HAART) and often neutrophil growth factors (A is *false*). HIV-associated Hodgkin lymphoma causes stage IV disease much more often than non-HIV-associated disease (C is *false*). Although HIV-associated non-Hodgkin lymphoma is linked to a markedly increased risk for CNS involvement, the same has not been noted with Hodgkin lymphoma.

Ch / 187 PLASMA CELL DISORDERS

1. A 63-year-old man is found to have a serum monoclonal protein level of 1.6 g/dL during work-up of joint pains. The monoclonal protein is IgG κ on immunofixation. He has no anemia, hypercalcemia, renal failure, or bone lesions. Bone marrow biopsy shows 8% plasma cells. The most likely diagnosis is

- A. Multiple myeloma
- B. Smoldering multiple myeloma
- C. Monoclonal gammopathy of undetermined significance (MGUS)
- D. Idiopathic Bence Jones proteinuria
- E. Waldenström's macroglobulinemia

Answer: C This patient has a small monoclonal protein, without evidence of end-organ damage. This could be either MGUS or smoldering myeloma. The bone marrow plasma cell percentage is less than 10%, and the serum monoclonal protein level is less than 3 g/dL. Thus the diagnosis is MGUS. In contrast to MGUS, smoldering multiple myeloma requires either 10-60% plasma cells on bone marrow or 3 g/dL or more M spike on serum protein electrophoresis. The diagnosis of myeloma requires presence of one or more myeloma defining events. (See Table 187-2.)

2. Which of the following are risk factors for progression in monoclonal gammopathy of undetermined significance?

- A. Size of the M protein
- B. Type of the M protein
- C. Abnormal free light chain ratio
- D. A and C
- E. A, B, and C

Answer: E The best predictors of progression of MGUS are the size of the M protein, the type of the M protein, and an abnormal baseline free light chain ratio. Patients with a serum M protein of less than

1.5 g/dL, IgG type, and normal free light chain ratio have a 5% probability of progression during 20 years. In contrast, if all three factors were abnormal, the risk of progression during that time is in excess of 50%. Another predictor of progression has recently been reported: reduction of one or two noninvolved immunoglobulin isotype levels (immunoparesis). (See section on prognosis under MGUS.)

3. Autologous stem cell transplantation is commonly used in the treatment of multiple myeloma in eligible patients. Which of the following statements is true about this procedure for the treatment of myeloma?

- A. It is less commonly used more recently as therapy for myeloma compared with nonmyeloablative allogeneic transplantation.
- B. It is not curative but prolongs overall and event-free survival.
- C. Patients typically receive four to six cycles of melphalan, prednisone, and bortezomib (VMP) before transplantation.
- D. Patients typically receive four to six cycles of thalidomide, melphalan, and prednisone (MPT) before transplantation.
- E. The typical conditioning regimen is total body irradiation plus high-dose melphalan.

Answer: B Autologous stem cell transplantation for myeloma is not curative. Transplantation prolongs overall and event-free survival by about 12 to 18 months. It is much more commonly used than nonmyeloablative allogeneic transplantation, which should still be considered investigational for this disease. Melphalan should be avoided before induction because it may affect stem cells and prevent adequate mobilization; therefore, VMP and MPT are not good options before transplantation. The typical conditioning regimen is melphalan 200 mg/m².

4. Which of the following agents is associated with a high risk of peripheral neuropathy?

- A. Bortezomib
- B. Lenalidomide
- C. Pomalidomide
- D. Carfilzomib
- E. Melphalan

Answer: A Of the agents listed, bortezomib is the drug associated with the highest risk of neuropathy. The major adverse effects with lenalidomide and pomalidomide include thrombosis, rash, low blood counts, and fatigue. Carfilzomib is a new proteasome inhibitor that unlike bortezomib appears to have less risk of neuropathy. Melphalan is an alkylating agent that is associated with low blood counts and risk of myelodysplastic syndrome. The rate of bortezomib neuropathy and its severity can be limited by use of a once-weekly dosing schedule and the subcutaneous route of administration. (See section on treatment of relapsed refractory myeloma under prevention and treatment of multiple myeloma.)

5. Which of the following is *not* true of Waldenström macroglobulinemia?

- A. The type of monoclonal protein in Waldenström macroglobulinemia tends to form a pentamer.
- B. Most patients have a mutation of the *MYD88* gene (MYD88 L265P).
- C. Hyperviscosity is an important feature of the disease.
- D. Osteosclerotic bone lesions are seen in 25% of patients.
- E. Rituximab, cyclophosphamide, dexamethasone (RCD) is a commonly used treatment regimen.

Answer: D Osteosclerotic bone lesions are a feature of the POEMS syndrome, not of Waldenström's macroglobulinemia. Unlike with myeloma, in which osteolytic bone disease is present in most patients, patients with Waldenström's macroglobulinemia do not have bone disease. The type of monoclonal protein is IgM; this molecule tends to pentamerize, and the high molecular weight leads to hyperviscosity. Rituximab, cyclophosphamide, dexamethasone (RCD) is a commonly used treatment regimen for initial therapy. (See section on Waldenström macroglobulinemia.)

1. A 61-year-old man presents to an otorhinolaryngologist with hoarseness. During laryngoscopy, a mass is found on the left vocal cord. A biopsy specimen shows dense deposits of amyloid. The patient is referred to you for subsequent evaluation. What is the most likely next step?

- A. Cardiac biopsy to assess suitability for high-dose chemotherapy and stem cell transplantation
- B. Initiation of bortezomib-based chemotherapy
- C. Bone marrow biopsy to determine whether this represents coexistent multiple myeloma
- D. Referral back to the otorhinolaryngologist for therapy
- E. Bronchoscopy to assess status of mainstem bronchi

Answer: D Laryngeal and vocal cord amyloid is always localized (not associated with systemic amyloid). Therefore, the treatment is local and usually involves endoscopic laser therapy of the amyloid deposits. Recurrence is common, and the patient is likely to require ongoing monitoring. Pulmonary function testing would be reasonable to detect flow obstruction. Computed tomography imaging would not add value to the evaluation.

2. A 76-year-old black man is referred to you by a cardiologist after an endomyocardial biopsy specimen showed amyloid deposits. The patient was seen for dyspnea on exertion that evolved during 24 months. The echocardiogram was clinically suggestive of infiltrative cardiomyopathy. The patient has congestive heart failure. Serum and urine immunofixation assays were negative, and a free light chain assay showed a normal ratio. What should be your next step in the evaluation?

- A. Classify the amyloid by mass spectrometry.
- B. Chemotherapy is urgent in the presence of progressive congestive heart failure.
- C. If a bone marrow assay is negative for amyloid deposits, the patient is eligible for cardiac transplantation.
- D. Computed tomography imaging of the chest, abdomen, and pelvis should be performed to screen for occult amyloid deposits.

Answer: A The absence of serum and urine light chains and a normal light chain ratio make light chain amyloidosis highly unlikely. This patient is more likely to have non-immunoglobulin-related amyloidosis. Three percent of black men have a mutation in transthyretin, which causes late-onset familial amyloid cardiomyopathy. At 76 years of age, senile cardiac (systemic) amyloidosis is a definite possibility. There is a 1% possibility that this is light chain amyloidosis. The evaluation cannot move forward until the type of amyloid is identified. Mass spectrometry is the method most likely to provide this information (see reference 2).

3. Your patient with renal amyloidosis read that cerebral amyloid angiopathy is found in most patients with Alzheimer disease. The patient is concerned that dementia will soon follow. What is your next step?

- A. Referral to a neurologist for neurocognitive studies
- B. Magnetic resonance imaging to look for cerebral amyloid angiopathy
- C. Aspirin therapy to prevent subcortical infarcts
- D. Tell the patient not to worry

Answer: D The amyloid in Alzheimer disease is composed of amyloid- β protein, which is chemically unrelated to immunoglobulin light chains. There is no increased risk of Alzheimer disease in the patient.

4. A 58-year-old man is referred to you with endomyocardial biopsy-proven amyloidosis. The λ monoclonal protein in the serum is 0.6 mg/dL. The κ/λ free light chain ratio is 0.01. You perform a bone marrow biopsy that shows 7% plasma cells. The serum troponin level is 0.08 ng/mL. The N-terminal pro-brain natriuretic peptide value is 7800 pg/mL. What is your recommendation?

- A. Referral to a transplant center for high-dose therapy
- B. Referral for cardiac transplantation
- C. Initiation of conventional chemotherapy
- D. Initiation of digoxin to prevent atrial fibrillation
- E. Referral for consultation in palliative care

Answer: C This patient's cardiac biomarkers suggest a degree of cardiac dysfunction that is associated with an excessive risk of death during a transplant procedure. This patient cannot be considered for cardiac transplantation until the underlying hematologic disorder is under control. Even patients with advanced cardiac failure can have improvement of cardiac function with appropriate systemic chemotherapy. Digoxin is contraindicated in cardiac amyloidosis.

5. Which is (are) the most important test(s) for assessing prognosis in a patient with light chain amyloidosis?

- A. Troponin
- B. Free light chains
- C. N-terminal pro-brain natriuretic peptide
- D. β 2-Microglobulin
- E. Fluorescence in situ hybridization (genetic test)
- F. A through C
- G. B and D
- H. A and C
- I. A through D
- J. A through E

Answer: F The cardiac biomarkers (troponin and N-terminal pro-brain natriuretic peptide) determine the prognosis in this disease and are the most important tests to perform. Testing for free light chains would complete the evaluation of prognosis as a measure of tumor mass. β 2-Microglobulin and albumin are not important markers for light chain amyloidosis, although they are important in multiple myeloma. The role of genetics is presently undefined in amyloidosis, and very few patients carry the adverse t(4;14) and -17p chromosomal abnormalities seen in myeloma.

1. A 78-year-old woman is brought to the hospital by her family, who are complaining that she has lost interest in her usual activities and appears depressed during the past 4 to 6 months. She was started on an antidepressant by her internist 3 months ago without any response. They have also noticed that her walking has deteriorated in the past month, and in the last week she has developed incontinence. On examination, you find she is indifferent and has a flat affect and bilateral frontal release signs. She shuffles when she walks and her balance is poor. You order magnetic resonance imaging (MRI), which shows a large bifrontal diffusely enhancing tumor compressing the frontal lobes without much underlying edema; a dural tail is evident. The tumor type is likely to be

- A. Glioblastoma
- B. Meningioma
- C. Metastasis
- D. Primary CNS lymphoma
- E. Anaplastic oligodendroglioma

Answer: B Meningiomas can grow to a huge size without causing problems because they grow so slowly and the underlying brain accommodates the compression. Subacute onset of social withdrawal in an older patient should always be suggestive of an underlying neurologic process, particularly when other findings, such as a gait disorder and incontinence, are apparent; all these symptoms can be caused by compression of both frontal lobes. Resection can completely remove this tumor and restore the patient to normal function, and she is unlikely to experience recurrence. (Rocha H, Cerejo A, Garrett MC, Massano J. Reversible parkinsonism due to a large intracranial tumour. *BMJ Case Rep.* 2012; pii: bcr2012007823.)

2. A 56-year-old man with lung cancer comes to the emergency department complaining of progressively severe upper back pain that can occasionally radiate around his chest. The pain increases with cough or Valsalva maneuver. He has no sensory or motor symptoms. His examination reveals no neurologic deficits. The next step in evaluating his pain is

- A. Spine radiograph
- B. Chest radiograph
- C. Bone scan
- D. Treat with pain medications and observe
- E. Spine MRI

Answer: E This patient has a high likelihood of having metastases to the spinal column. The pain is located in the upper back, which is atypical for the common musculoskeletal causes of back pain, and the pain radiating around his chest suggests compression of the thoracic nerve roots; exacerbation of the pain with cough or Valsalva maneuver indicates compression on the thecal sac. Imaging is essential, so observation is not an option, and plain radiographs or bone scan cannot visualize tumor extending into the epidural space. A complete spine MRI study was obtained and demonstrated marked epidural tumor with spinal cord compression at T6. Because it was a single site of disease and the patient had few comorbidities, he had a complete resection followed by focal radiation therapy and did well.

3. A 72-year-old man has a history of prior myocardial infarction, congestive heart failure, atrial fibrillation with anticoagulation, and metastatic renal cell cancer. He was at home when he had the sudden onset of left hand twitching that progressed to involve his whole arm and the left side of his face. It stopped after 45 seconds, and he had mild weakness of his left arm and hand, which resolved completely during 12 hours. He went to the local emergency department, where MRI revealed a single enhancing mass 1×0.8 cm in the right frontal lobe with surrounding edema, consistent with a metastasis. What is the best therapeutic approach in this man with poor renal function and severe cardiac disease?

- A. Supportive care only
- B. Surgical resection
- C. Whole brain radiation therapy
- D. Stereotactic radiosurgery
- E. A change in chemotherapy

Answer: D This is a single brain metastasis in a patient with a primary tumor type that is relatively radioresistant. Furthermore, he is older and likely to experience greater neurologic toxicity if his whole brain is irradiated, so whole brain radiation therapy is a poor option. Resection could be considered, but his medical condition is too poor for surgery. Chemotherapy is unlikely to be effective for a brain metastasis from renal cancer. Stereotactic radiosurgery is an excellent option. The tumor is small and therefore a good candidate for this approach. Relatively radioresistant primaries respond better to the single high-dose fraction of stereotactic radiosurgery; it is also easy to administer, and with a good response the patient is more likely to discontinue steroids and avoid their attendant toxicities. Supportive care could be a reasonable option, but given that his brain metastasis has never been treated and stereotactic radiosurgery has a high probability of being efficacious with minimal toxicity, it is the best option.

4. A 67-year-old right-handed woman comes to your office complaining of several episodes during the past 2 months of the abrupt onset of an inability to speak. She knows what she wants to say but is unable to get the words out. These episodes can last for about 1 minute and then resolve and she is normal. In addition, in the past 2 to 3 weeks, she has noticed progressive word finding difficulty and occasional word substitutions and very mild headache during the past few days. MRI reveals a contrast-enhancing mass in the left temporal lobe. She has a surgical resection, and the pathologic examination reveals a glioblastoma. The next steps in her treatment are
- A. Radiation therapy with concurrent and adjuvant temozolomide
 - B. Radiation therapy alone
 - C. Temozolomide alone
 - D. No further treatment after resection
 - E. Radiation therapy, temozolomide, and bevacizumab

Answer: A Despite a complete resection, a glioblastoma requires additional therapy after surgery because there are always infiltrative cells left behind even when postoperative MRI shows that all the enhancing disease was removed. A large phase III trial has established that the standard of care for a newly diagnosed glioblastoma includes focal radiation therapy with concurrent and adjuvant temozolomide. This is clearly superior to either modality alone. Two recent studies demonstrated that the addition of bevacizumab to radiation therapy and temozolomide failed to improve survival, so it is not included in the initial regimen.

1. The most important prognostic biomarker in squamous cell cancer of the head and neck is

- A. Cytomegalovirus
- B. Human papillomavirus
- C. Herpes simplex virus
- D. Merkel cell tumor virus
- E. All of the above

Answer: B Human papillomavirus (HPV) is the single most important prognostic biomarker in squamous cell cancer of the head and neck. Patients with HPV cancers have a three-fold better survival than that of patients with cancers caused by environmental factors. Patients with HPV-related cancers also have fewer comorbid illnesses and less risk of second primaries.

2. The patient and the physician should discuss the possibility of organ-preserving therapy for patients with hypopharynx and larynx cancers. Some of the accepted strategies for organ preservation are

- A. Chemoradiotherapy
- B. Partial laryngectomy
- C. Sequential therapy
- D. Radiation therapy
- E. All of the above

Answer: E All three treatments are reasonable larynx-preserving treatments, depending on stage, comorbidities, and lymph node involvement. For early-stage tumors in which radiation therapy may be avoided, partial surgery is indicated. For more advanced cancers, radiation therapy only or a combination of chemotherapy and radiation therapy is indicated. Laryngectomy is a reasonable therapy when the patient cannot tolerate treatment, is noncompliant, or already has a nonfunctional larynx.

3. Postoperative adjuvant cisplatin-based chemoradiotherapy is absolutely indicated for

- A. Lymphovascular invasion
- B. A positive margin
- C. Perineural invasion
- D. Extracapsular lymph node extension
- E. Both B and D

Answer: E After surgery, pathologic findings of a positive margin and extracapsular lymph node extension are absolute indications for postoperative cisplatin-based adjuvant chemoradiotherapy if the patient can tolerate therapy. Lymphovascular invasion and perineural invasion are less robust criteria and can justify adjuvant chemoradiotherapy. Postoperative chemoradiotherapy is associated with a significant improvement in locoregional control and a trend to improved survival at 10 years.

4. What therapeutic biomarker is associated with prognosis in salivary ductal carcinoma?

- A. EGFR1 expression
- B. Her2 expression
- C. Androgen receptor
- D. *PTEN* deletion
- E. Both B and C

Answer: E Salivary ductal carcinomas can express either Her2 or androgen receptor (AR). Her2-positive salivary ductal carcinoma will respond to Her2- specific therapies and combinations with long survival, and similarly there are data to support use of AR antagonists in AR-positive salivary ductal carcinoma. No other biomarkers have been identified in salivary gland tumors.

5. An adult presenting with a persistent cervical neck mass should be presumed to have

- A. A throat infection
- B. A cancer until proven otherwise
- C. A branchial cleft cyst
- D. Mononucleosis
- E. Both B and C

Answer: B A neck mass, cystic or otherwise, presenting in an adult should be presumed to be cancer until proven otherwise. Even a normal finding on fine-needle aspiration is insufficient to rule out malignant disease. Patients should be worked up extensively before neck dissection.

Ch / 191 LUNG CANCER AND OTHER PULMONARY NEOPLASMS

1. Which of the following individuals should not consider computed tomography (CT) screening for lung cancer because of an absence of increased risk?

- A. Individuals who are older than 55 years and have at least 35 pack-years of smoking cigarettes
- B. A woman with a heavy smoking history (more than 50 pack-years) and evidence for emphysema/chronic obstructive pulmonary disease
- C. A former smoker who is 70 years old with a 60 pack-year history but who quit smoking 5 years ago
- D. A patient with a prior history of laryngeal cancer treated by chemotherapy and radiation therapy, with a 40 pack-year history, who is down to one or two cigarettes per day
- E. A 35-year-old man whose father died of lung cancer after a long smoking history

Answer: E There is no evidence that nonsmoking individuals who have family histories of lung cancer, particularly lung cancer that is attributable to smoking, will benefit by being screened with CT scans. The best evidence to date for the utility of CT screening is for individuals older than 55 years with at least a 30 to 35 pack-year smoking history. These individuals are more likely to have a nodule detected by CT scan than by chest radiography, as shown by the NLST study. Thus, individuals A, B, C, and D, all of whom are older than 55 years and have at least a 30 to 35 pack-year smoking history, are at increased risk for lung cancer, and all could potentially benefit from screening with CT scan.

2. Which of the following is most consistent with a tissue diagnosis of a lung adenocarcinoma?

- A. TTF-1 positive, CK7 positive, EGFR driver mutation, and CK20 negative and p63 negative
- B. TTF-1 negative, p63 positive, p40 positive, FGFR amplification, and EGFR wild type
- C. Synaptophysin and chromogranin positive, p53 mutation and Rb mutation
- D. Tumor positive for vimentin and melanin, negative for TTF-1 and for all cytokeratins
- E. CD20 positive, negative for TTF-1 and for all cytokeratins

Answer: A Patients with lung adenocarcinoma are likely to have a TTF-1– positive tumor, with CK7 expressed. CK20 is more commonly expressed in colorectal cancers than in lung tumors. The fact that p63 is negative in this case makes this less likely to be a squamous cell carcinoma. The clearest indicator here is that the patient has an EGFR driver mutation. Mutations in exons 19 or 21 of EGFR are pathognomonic for lung adenocarcinoma, particularly in never-smokers. The other three cases are all less likely to be adenocarcinomas. Case B is p63 positive, which makes it more likely to be squamous cell cancer, and all the other features, including being p40 positive and FGFR amplification, are more frequently seen in squamous cell cancers. EGFR is mutated almost exclusively in lung adenocarcinomas as opposed to squamous cell carcinomas, although the fact that this case B is wild type does not make it less likely to be an adenocarcinoma. Case C is more likely to be a small cell carcinoma, as synaptophysin and chromogranin are positive for neuroendocrine tumors, and the combination of the p53 and Rb mutations makes this likely to be a small cell lung cancer. In case D, the tumor is positive for vimentin and melanin and negative for TTF-1 and all cytokeratins; this is not an epithelial tumor and is likely to be a melanoma or poorly differentiated sarcoma. The tumor in E

that is CD20 positive is likely to be a lymphoma, and this is again negative for cytokeratins that are expressed on epithelial tumors as well as for TTF-1, which would make this highly unlikely to be an epithelial tumor in general and a lung cancer in particular.

3. A 63-year-old woman with a heavy smoking history presents with a diagnosis of a squamous cell lung cancer, staged radiographically as T3N2M0. She has been referred to a thoracic surgeon who is planning to perform a mediastinoscopy. If the mediastinoscopy confirms the presence of tumor cells in her mediastinal lymph nodes, the best recommendation for the multidisciplinary clinic is
- A. Surgical resection of her tumor by a pneumonectomy and clearing of her mediastinum followed by radiation therapy to any positive margins
 - B. Induction or preoperative chemotherapy followed by radiation therapy followed by surgery
 - C. Concurrent chemotherapy and radiation therapy
 - D. Induction chemotherapy followed by radiation therapy
 - E. Palliative chemotherapy followed by hospice referral

Answer: C This is the presentation of a patient with stage 3A non-small cell lung cancer. A patient such as this with a good performance status would best be treated with concurrent chemotherapy and radiation therapy, which would give a 15 to 20% chance of 5-year survival. Surgical resection of the tumor by pneumonectomy and clearing of the mediastinum followed by radiation therapy is a highly morbid procedure and a particularly poor choice, given that the mediastinal lymph nodes are involved. This patient is at least as likely to fail at distant sites as in the mediastinum, and chemotherapy is as essential as radiation therapy to this patient. Option B is suboptimal in that randomized trials have shown that concurrent chemotherapy and radiation therapy is superior to induction or preoperative chemotherapy followed by radiation therapy. Following chemotherapy and radiation therapy with surgery is controversial, with evidence that patients receiving this trimodality therapy with all but the most limited mediastinal lymph nodes are more likely to do poorly. Option D is again inferior to option C as randomized trials have shown over time. Answer E is the most inappropriate of all. This is a patient with a 15 to 20% chance for a cure, and it is inappropriate to treat her with palliative chemotherapy followed by hospice referral, as long as the patient's performance status is good and the patient is willing to be treated fully in an attempt at cure.

4. A 70-year-old man with lung adenocarcinoma, diagnosed as stage IVB (T2N2M1) with metastases to the lymph nodes, bilateral adrenal glands, and liver, presents with an excellent performance status, an Eastern Cooperative Oncology Group (ECOG) status 1. He has never received prior chemotherapy for his lung cancer. He has no evidence of a driver mutation on genomic analysis of his tumor. Which of the above is *not* an acceptable approach to his management?
- A. Combination chemotherapy with carboplatin, paclitaxel, and bevacizumab
 - B. Combination therapy with carboplatin and pemetrexed
 - C. Combination chemotherapy with supportive care initiated at the time of the first visit
 - D. Single-agent paclitaxel plus erlotinib, the EGFR tyrosine kinase inhibitor
 - E. A second opinion followed by participation in a frontline clinical trial combining chemotherapy and immunotherapy

Answer: D This question describes a patient with good performance status who does not have a driver mutation that would increase the likelihood of benefiting from frontline targeted therapy. As such, there are many reasonable options, all of them starting with platinum-based chemotherapy. ECOG-5597 showed that the combination of carboplatin, paclitaxel, and bevacizumab was associated with a median survival of more than 12 months, and studies with combination therapy with cisplatin or carboplatin and pemetrexed indicate similar survivals. Option C may be the best option of all, as recent data indicate that combination chemotherapy with early initiation of supportive care appears to be associated with a survival advantage. Finally, option E is also an excellent one with evidence that patients who do not have curable disease should strongly consider participating in a frontline clinical trial, in this case, combining immunotherapy and chemotherapy. In fact, the only inappropriate option

is D, which is the correct answer to this question. Patients with lung cancer benefit from combination chemotherapy, and there is little evidence that combining paclitaxel with a small-molecule EGFR inhibitor such as erlotinib provides equivalent benefit to combination chemotherapy alone. Therefore, in the absence of a driver *EGFR* mutation, all options are acceptable, making D the only wrong choice.

5. A 50-year-old never-smoking woman presents with a headache followed by a seizure. Her emergent work-up reveals a solitary brain lesion, which is resected and reveals lung adenocarcinoma containing an EGFR driver mutation in exon 19. After consideration of radiation therapy to the brain, the optimal treatment approach would be
- A. Combination chemotherapy with carboplatin, paclitaxel, and bevacizumab
 - B. Combination therapy with carboplatin and pemetrexed
 - C. Combination chemotherapy with supportive care initiated at the time of the first visit
 - D. Initiation of erlotinib, the EGFR tyrosine kinase inhibitor
 - E. A second opinion followed by participation in a frontline clinical trial combining chemotherapy and immunotherapy

Answer: D This question describes a woman who has an *EGFR* mutation– driven lung cancer. She presents with a solitary brain lesion and is treated. The patient may well benefit from radiation therapy, either stereotactic radiation to the residual lesion or whole brain irradiation, but it is clear that the optimal therapy for her, based on the randomized trial published by Mok [A3](#) along with an abundance of other data, is to initiate her treatment with erlotinib or gefitinib, first-generation tyrosine kinase inhibitors, which, in this population of patients, are far more active than chemotherapy combinations. Therefore, option D, given the documented *EGFR* mutation, is superior to options A, B, and C. Finally, whereas E is reasonable from the perspective that all patients with lung cancer should strongly consider a second opinion, this patient is far more likely to benefit from erlotinib or other EGFR tyrosine kinase inhibitors than from chemotherapy and immunotherapy.

1. What is a leading risk factor for the development of Barrett’s esophagus and esophageal adenocarcinoma?
- A. Obesity
 - B. Nutritional deficiencies
 - C. Childhood gastroesophageal reflux disease
 - D. High-fiber diet

Answer: A Obesity, specifically central adiposity, has been associated with increased risk of Barrett’s esophagus and esophageal adenocarcinoma in separate studies. Mechanistically, there is secretion of cytokines and chemokines from adipocytes that likely produce pro-inflammatory states in the esophagus in both conditions.

2. What is a key risk factor for the development of gastric adenocarcinoma?
- A. Obesity
 - B. *Helicobacter pylori* infection
 - C. History of pancreatic cancer
 - D. Blood group O

Answer: B *Helicobacter pylori*, a common organism worldwide that affects nearly 2 billion individuals, causes gastric atrophy with achlorhydria and subsequent intestinal metaplasia in the gastric epithelium. This can evolve to dysplasia (low grade and high grade) and adenocarcinoma, so-called intestinal type. Note that only a subset of chronically *H. pylori*–infected patients progress to gastric adenocarcinoma, suggesting other cofactors are important.

3. Therapy of esophageal or gastric cancer may involve all the following modalities *except*:

- A. Surgery
- B. Chemoradiation therapy
- C. Palliative chemotherapy
- D. Bone marrow transplantation

Answer: D Bone marrow transplantation is not an option. The modalities in A, B, and C are all used and dictated by the stage of esophageal or gastric cancer.

4. What hereditary condition predisposes to gastric adenocarcinoma?

- A. Germline *E-cadherin* mutation
- B. Germline *TP53* mutation
- C. Germline *p16INK4a* mutation
- D. Germline *p120* catenin mutation

Answer: A Germline E-cadherin mutation predisposes to early-age onset of diffuse hereditary gastric adenocarcinoma and may also be associated with lobular-type breast cancer.

5. What is a likely treatment option for Barrett's esophagus with high-grade dysplasia and no surrounding esophageal adenocarcinoma?

- A. Neoadjuvant chemoradiation therapy
- B. Laser therapy
- C. Endoscopic mucosal resection (EMR)
- D. Endoscopic prosthetic stent

Answer: C Endoscopic mucosal resection (EMR) is a viable option for high-grade dysplasia, as well as intramucosal esophageal adenocarcinoma. Radiofrequency ablation via endoscopy is used for low-grade dysplasia Barrett's esophagus and may be used for high-grade dysplasia Barrett's esophagus under certain circumstances.

Ch / 193 NEOPLASMS OF THE SMALL AND LARGE INTESTINE

1. A 55-year-old average-risk patient undergoes a screening colonoscopy. There is no family history of polyps or colorectal cancer, and the patient is asymptomatic. A single 6-mm tubular adenoma was found in a well-prepared and otherwise normal colonoscopy. The next colonoscopy should be performed at:

- A. 1 year
- B. 2 years
- C. 3 years
- D. 5-10 years
- E. Never. Surveillance is not indicated.

Answer: D For average-risk patients with otherwise normal colonoscopies, the finding of a single nonadvanced tubular adenoma (<10 mm, no villous histology or high-grade dysplasia) requires a next colonoscopy to be performed at 5-10 years. (See section on "Prognosis" under "Adenomatous Polyps.")

2. A patient with colorectal cancer (CRC) is found to have microsatellite instability on testing of the resected tumor. There is a strong family history of CRC, including a parent and a sibling. Germline mutation analysis is performed and finds a mutation in one of the mismatch repair genes (*MLH1*). This patient most likely has:

- A. Hereditary nonpolyposis colorectal cancer (Lynch syndrome)
- B. Familial adenomatous polyposis
- C. *MUTYH*-associated polyposis
- D. CpG island methylation (CIMP)
- E. *BRAF* mutation

Answer: A Mutations in the mismatch repair genes (*hMSH2*, *hMSH3*, *hMSH6*, *hMLH1*, *hPMS1*, and *hPMS2*) result in errors in DNA replication. These errors can be detected as microsatellite instability in the resected tumor. Errors in these genes result in hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome. (See section on “Hereditary Nonpolyposis Colon Cancer.”)

3. The most important factor in deciding whether to offer adjuvant chemotherapy following potentially curative resection of colon cancer is:

- A. Tumor size
- B. Tumor grade
- C. Patient age
- D. Patient gender
- E. Tumor stage

Answer: E Although multiple factors are prognostic and/or predictive, stage is the most important determinant in the decision regarding adjuvant systemic therapy. (See section on “Systemic and Combination Therapies” under “Treatment” of “Adenocarcinoma of the Colon and Rectum.”)

4. Reasonable agents to offer a patient with resected stage III colon cancer include:

- A. 5-Fluorouracil
- B. Oxaliplatin
- C. Irinotecan
- D. A and B
- E. A, B, and C

Answer: D All the listed agents have activity in metastatic disease, but irinotecan has not been proven to offer any benefit in the adjuvant setting. (See section on “Systemic and Combination Therapies” under “Treatment” of “Adenocarcinoma of the Colon and Rectum.”)

5. A major difference between colonic and rectal adenocarcinoma is:

- A. Treatment of metastatic disease
- B. Underlying genetic makeup
- C. Frequency of use of irradiation
- D. Frequency of complications of an intact primary in the setting of treated metastatic disease
- E. C and D

Answer: E Colonic and rectal cancers are for the most part biologically similar, including sensitivity to systemic agents. Because of anatomic concerns, treatment of higher-risk rectal cancer almost always involves irradiation, whereas that modality is seldom used in treating colon cancer. Similarly, rectal cancers have a slightly higher chance of bleeding or obstructing if not undergoing primary treatment.

1. Which of the following is not a known risk factor for pancreatic cancer:

- A. Chronic proton pump inhibitor therapy
- B. Positive family history
- C. Cigarette smoking
- D. Obesity
- E. Chronic pancreatitis

Answer: A Gastrectomy, much more commonly performed in the past for refractory peptic ulcer disease, was considered to be a risk factor for pancreatic cancer; however, there is no evidence that medical therapy for it (e.g., with proton pump inhibitors) poses a risk. Approximately 10% of pancreatic cancer cases occur in families with a positive history. Cigarette smoking, even second-hand, has been clearly linked to pancreatic cancer risk. Obesity is associated with increased risk for a variety of cancers, including pancreatic. The long-known risk of pancreatic cancer with chronic pancreatic inflammation is now being elucidated at the molecular level as a function of the action of pro-inflammatory cytokines on progression from pre-malignant lesions to advanced tumor. (See section on "Epidemiology.")

2. Which of the following is not known to be a clinical manifestation of pancreatic cancer:

- A. Diabetes mellitus
- B. Courvoisier's sign
- C. Superficial thrombophlebitis
- D. Splenic infarction
- E. Obstructive jaundice

Answer: D The symptoms of early pancreatic cancer are often subtle, and there may be no abnormal findings on physical exam. Although extensive pancreatic cancer could potentially cause portal vein or splenic vein thrombosis, compromise of the spleen's arterial supply to cause splenic infarction is not characteristic. Hyperglycemia and even frank clinical type 2 diabetes mellitus may be a harbinger of occult pancreatic cancer, and its onset may antedate the cancer diagnosis by months. Courvoisier's sign, a palpably distended gallbladder, is a striking physical finding resulting from distal common bile duct obstruction due to pancreatic cancer, although it is very rare. Obstructive jaundice that is often painless is, however, not an uncommon presenting manifestation because 75% of pancreatic cancers are located in the head of the pancreas. Superficial thrombophlebitis, particularly when it is migratory in nature (called Trousseau syndrome) is frequently a sign of occult cancer, with pancreatic cancer being among the most common.

3. Which of the following approaches provides the best results in increasing survival after surgery for pancreatic cancer:

- A. Radiation therapy
- B. Combined chemoradiation therapy and chemotherapy
- C. Gemcitabine or 5-fluorouracil
- D. Biologic agents
- E. Unfortunately, no current therapy increases survival after surgery.

Answer: C A recently published meta-analysis of several clinical trials has shown that chemotherapy with 5-fluorouracil or gemcitabine is the currently optimum adjuvant treatment for pancreatic adenocarcinoma and reduces mortality after surgery by about a third. Adjuvant radiation therapy alone or combined chemoradiation and chemotherapy are less effective in prolonging survival and are more toxic than chemotherapy with 5-FU or gemcitabine. Biologic agents are not known to be effective at this time.

1. Which is not a typical pathologic feature of most pancreatic neuroendocrine tumors (pNETs)?

- A. Stain for chromogranin
- B. Stain for synaptophysin
- C. Stain for neuron-specific enolase
- D. Have features of APUDomas
- E. Show moderate to increased mitoses

Answer: E Most pNETs show few mitoses, whereas most stain for all the other listed items, and they are historically classified as APUDomas owing to their staining characteristics.

2. Which molecular change is not generally involved in the pathogenesis of pNETs?

- A. Mutations of oncogenes
- B. Mutations in the *MEN1* gene
- C. Mutations in the DAXX-ATRX complex genes
- D. Mutations/alterations in the mTOR pathway
- E. Alterations in the *p16* gene

Answer: A In contrast to adenocarcinomas of the pancreas, mutations in common oncogenes (*ras*, *c-Jun*, etc.) or in common tumor suppressor genes (*p53*, retinoblastoma) are uncommon in pNET. In contrast, each of the other changes occurs in pNETs.

3. A 49-year-old man with abdominal pain is referred to you, and on laboratory evaluation is found to have a serum gastrin level of 35,000 pg/mL (normal, <100). Which of the following is true?

- A. Diagnosis of Zollinger-Ellison syndrome (ZES) is likely.
- B. Diagnosis of ZES syndrome is certain.
- C. Diagnosis of ZES is possible.
- D. Imaging studies should be performed next.
- E. Upper GI endoscopy should be the next study to establish ZES.

Answer: C No level of elevation of fasting gastrin alone establishes the diagnosis of ZES, no matter how high. Other diseases, particularly atrophic gastritis or pernicious anemia, which are much more frequent, can give fasting gastrin levels in this range. The next study to perform to rule out these latter possibilities is to measure the gastric pH and establish that it is 2 or less when the fasting serum gastrin is elevated.

4. Diarrhea is not a presenting symptom of which pNETs:

- A. Zollinger-Ellison syndrome
- B. VIPoma
- C. Glucagonoma
- D. Somatostatinoma
- E. GRFoma

Answer: E GRFomas characteristically present with acromegaly due to ectopic secretion of GRF, and diarrhea is not a feature. Each of the other pNETs not infrequently present with diarrhea as a feature.

5. Which of the following treatments is not commonly used to treat metastatic progressive pNETs?

- A. Streptozotocin ± 5-fluoruracil ± doxorubicin
- B. Somatostatin analogues
- C. Surgery if most (usually > 90%) of the metastatic tumor can be removed
- D. High-dose radiation to the hepatic metastases
- E. Liver-directed therapies such as embolization

Answer: D Radiation to the liver is not used, whereas each of the other modalities is used at different points to treat patients with progressive metastatic pNETs.

1. Which of the following descriptions is sufficient for the diagnosis of HCC without biopsy?
 - A. There is no exception to the requirement for histologic diagnosis for HCC. A biopsy is always required to confirm malignant cells are present.
 - B. An Asian man with known hepatitis B virus (HBV) infection without cirrhosis who is found to have a 3-cm, space-occupying lesion in the liver and an α -fetoprotein (AFP) value of 400 ng/mL.
 - C. A patient with Child-Pugh C cirrhosis as a result of long-standing HCV infection who develops hepatic decompensation along with the finding of an infiltrative, ill-defined mass on a liver ultrasound and α -fetoprotein value of 43 ng/mL compared to baseline AFP of 18 ng/mL 1 year earlier.
 - D. The presence of a tumor at least 1 cm in size arterial phase enhancement and hypoenhancement ("wash-out") in portal venous phase on contrast-enhanced CT or MRI scan in a patient with known liver disease.

Answer: D A nodule greater than 1 cm in patients with risk factors for HCC may be diagnosed radiographically as HCC without biopsy if there is arterial phase enhancement with decreased enhancement during the portal venous phase. AFP is not sufficient or necessary for diagnosis. (Reference: Bruix J, Sherman M, Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53:1020-1022.)

2. A 54-year-old man has Child-Pugh B cirrhosis as a result of HCV infection and a recent history of esophageal variceal bleeding requiring transfusion. He is radiographically diagnosed with a 2-cm HCC in the right lobe of the liver that demonstrates arterial enhancement and portal venous phase "wash out" on a contrast-enhanced CT scan. There is no evidence of vascular invasion or extrahepatic spread on imaging. Which of the following is the most appropriate management?
 - A. Percutaneous liver biopsy to confirm the diagnosis of HCC followed by referral to the interventional radiology department for transarterial chemoembolization (TACE)
 - B. Ablation or resection of the tumor followed by whole liver adjuvant radiation therapy
 - C. Referral to an expert center to evaluate for liver transplant
 - D. Surgical resection followed by adjuvant sorafenib
 - E. Watchful waiting

Answer: C This patient with Child-Pugh B liver dysfunction has a history of variceal bleeding suggesting significant portal hypertension, which indicates he is not an appropriate candidate for liver resection because of inadequate remnant liver function. There is no proved role for adjuvant radiation after resection or ablation. Watchful waiting is not an appropriate option in this patient at high risk for complications of liver dysfunction and/or tumor progression. Outcomes of liver transplant for cirrhotic patients with small HCC lesions are equivalent to those of cirrhotic patients without HCC. (References: Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334:693-699; Pelletier SJ, Fu S, Thyagarajan V, et al. An intention-to-treat analysis of liver transplantation for hepatocellular carcinoma using organ procurement transplant network data. *Liver Transplant*. 2009;15:859-868. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53:1020-1022.)

3. Sorafenib is currently the standard of care for patients with advanced stages of hepatocellular carcinoma. Which of the following statements is true about this drug?
 - A. Sorafenib is a selective inhibitor of c-Met tyrosine kinase that achieves prolonged time to progression in patients with advanced HCC whose tumors are positive for overexpression of c-Met by immunohistochemistry.
 - B. Sorafenib is a multikinase inhibitor, whose targets include VEGFR2 and Raf kinases, that has been shown to prolong survival in patients with incurable HCC in randomized, double-blinded, placebo-controlled phase III trials.
 - C. Sorafenib is a multikinase inhibitor that inhibits viral replication and can reverse the progression of cirrhosis, with increased benefit in patients with Child-Pugh B and C cirrhosis compared to Child-Pugh A cirrhosis.

- D. Sorafenib demonstrates improved outcomes in Asian patients with HBV-associated liver disease by comparison to non-Asian patients with underlying HCV infection as the cause of liver disease.
- E. Sorafenib is an immune-modulatory drug that stimulates effector T-cell responses against tumor antigens.

Answer: B Sorafenib is not a c-Met inhibitor nor an immune-modulatory drug. Patients with worse hepatic dysfunction experience greater toxicity and shorter survival on sorafenib therapy. Absolute survival outcomes on sorafenib appear poorer in Asian patients with underlying HBV than in non-Asian patients with underlying HCV. (References: Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359:378-390. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;10:25-34.)

4. A 47-year-old woman of South American descent undergoes laparoscopic cholecystectomy for a clinical diagnosis of cholelithiasis. After surgery, her pathology specimen is found incidentally to harbor adenocarcinoma of the gallbladder invading into the muscle layer (T1b) with negative margins. Staging imaging is negative for metastatic disease. Which of the following should be performed?
- A. No further treatment or observation is required after laparoscopic cholecystectomy.
- B. She should be followed with close observation including cross-sectional imaging and CA-19-9 tumor marker levels at approximately 6 month intervals for up to 5 years.
- C. She should be referred to a center with expertise in biliary tract cancers for hepatic resection and lymphadenectomy.
- D. She should be treated with adjuvant gemcitabine-based chemotherapy for 6 months.
- E. She should receive adjuvant radiation to the surgical resection bed.

Answer: C (Reference: Fuks D, Regimbeau JM, Le Treut YP, et al. Incidental gallbladder cancer by the AFC-GBC-2009 Study Group. *World J Surg*. 2011;35:1887-1897.)

5. A 71-year-old man previously in good health and without any known liver disease is found to have mildly elevated AST, ALT, and alkaline phosphatase, but normal bilirubin. He is asymptomatic without jaundice. An ultrasound shows a 4-cm right lobe liver mass along with two smaller right lobe lesions and one left lobe lesion, without significant biliary dilatation. Contrast-enhanced CT scans of the chest, abdomen, and pelvis show the same four hypoenhancing liver lesions during arterial phase, with no other abnormalities noted. A percutaneous CT-guided biopsy shows adenocarcinoma. Which is the most appropriate next step in management?
- A. Referral to a gastroenterologist for esophagogastroduodenoscopy (EGD) and colonoscopy to complete diagnostic evaluation.
- B. Referral to radiation oncology department for stereotactic beam radiation therapy for a diagnosis of unresectable, multifocal intrahepatic cholangiocarcinoma.
- C. Referral to an expert center to evaluate for liver transplant for intrahepatic cholangiocarcinoma.
- D. Referral to interventional radiology department for chemoembolization for a diagnosis of intermediate-stage bilobar hepatocellular carcinoma exceeding Milan criteria for transplantation.

Answer: A The clinical scenario describes multifocal adenocarcinoma lesions that could be due to intrahepatic cholangiocarcinoma with intrahepatic metastases, versus metastatic adenocarcinoma of another primary site, most commonly the gastrointestinal tract. Other primary adenocarcinoma tumors within the gastrointestinal tract that commonly metastasize to the liver (such as gastric and colon cancers) are not adequately evaluated by cross-sectional imaging and require EGD and colonoscopy to complete staging and guide treatment decision making. Although there may be a role for radiation for intrahepatic cholangiocarcinomas, the diagnosis must be confirmed before proceeding with radiation or chemotherapy. Liver transplantation is not an appropriate treatment for intrahepatic cholangiocarcinoma with multifocal liver lesions, nor for metastatic disease to the liver. Choice D is incorrect because the clinical vignette describes adenocarcinoma, not hepatocellular carcinoma, which has a histology different from that of adenocarcinoma.

1. A patient with muscle-invasive urothelial cancer of the bladder wishes to have bladder-sparing treatment with chemotherapy plus radiation. Which of the following components is critical to the success of the therapy?

- A. The radiation port includes the bladder, pelvic nodes, and a boost to the bladder.
- B. Brachytherapy to the primary tumor, followed by a boost to the entire bladder.
- C. Complete or near-complete transurethral resection of the bladder tumor (TURBT).
- D. Adjuvant chemotherapy for three cycles of cisplatin-based chemotherapy.
- E. Both A and C.

Answer: E A complete or near-complete TURBT is critical for success of this tri-modality approach (surgery, radiation, chemotherapy) to bladder-sparing treatment. Radiation is generally given to the bladder and pelvis, with a boost to the bladder cancer primary tumor.

2. A 56-year-old male patient with transitional cell carcinoma presents with carcinoma in situ involving the trigone of the bladder. The patient is treated with BCG therapy for two 6-week intervals without response. Repeat transurethral resection at 3 months shows persistent carcinoma in situ, along with new tumor invading the lamina propria but not the muscularis propria. The standard of care is:

- A. Radical cystectomy with preservation of the prostate and neurovascular bundle to preserve sexual function.
- B. Cystoprostatectomy and bilateral pelvic lymph node dissection.
- C. Intravesical interferon or interleukin-2.
- D. Systemic chemotherapy with a cisplatin-containing regimen.
- E. External beam radiation with a chemotherapy radiosensitizer.

Answer: B The standard of care for refractory carcinoma in situ is cystoprostatectomy and bilateral pelvic lymph node dissection. Refractory disease is defined in this instance as progression to a greater stage within 6 months of therapy.

3. Interleukin-2 (IL-2) therapy for patients with renal cell carcinoma differs from drugs that target vascular endothelial growth factor (VEGF) in that:

- A. IL-2 therapy can result in a 4% long-term cure in patients with metastatic disease.
- B. IL-2 therapy has a greater response rate than VEGF inhibitors.
- C. IL-2 therapy is given immediately after nephrectomy in contrast to VEGF inhibitors, which are given only for metastatic disease.
- D. IL-2 can be given in patients with poor renal function.
- E. IL-2 therapy is reserved for patients with brain metastases.

Answer: A The approval for IL-2 therapy by the U.S. Food and Drug Administration was, in part, based on this durability of complete responses in approximately 4% of patients, which is not seen with any other systemic treatments for metastatic renal cell carcinoma.

4. The preferred surgical management for a patient with a 7-cm renal cell carcinoma in one kidney and a simple cyst in the contralateral kidney includes:

- A. Bilateral nephrectomy.
- B. Open partial nephrectomy for the kidney with the 7-cm lesion.
- C. Nephrectomy for the kidney with the 7-cm lesion and retroperitoneal lymph node dissection
- D. Laparoscopic partial nephrectomy for the kidney with the 7-cm lesion.
- E. Answers B and D.

Answer: E Partial nephrectomy to preserve renal function as much as possible is the preferred surgical management in patients with renal cell carcinoma. Simple cysts of the kidney are observed, and a retroperitoneal lymph node dissection is not the surgical standard of care for renal cell carcinoma.

5. A patient presenting with benign hair follicle tumors (fibrofolliculomas), pulmonary cysts with a history of pneumothorax in the past, and bilateral renal tumors has which of the following syndromes?

- A. Hereditary papillary renal cell carcinoma (HPRCC)
- B. Hereditary leiomyomatosis renal cell carcinoma (HLRCC)
- C. Birt-Hogg-Dubé syndrome
- D. Familial oncocytoma
- E. Lynch syndrome

Answer: C Explanation: Birt-Hogg-Dubé syndrome is characterized by fibrofolliculomas, pulmonary cysts, pneumothorax, and bilateral of the renal tumors. Hereditary papillary renal cell carcinoma is associated with bilateral, multifocal tumors but not the other features. Hereditary leiomyomatosis renal cell carcinoma is associated with uterine leiomyomas (more common) or leiomyosarcoma (rare), cutaneous nodules (leiomyomas), and type 2 papillary renal cell carcinoma, which is frequently solitary and frequently develops metastases.

1. A 36-year-old woman presents with a palpable 2-cm right upper outer quadrant breast mass. There is no palpable axillary, cervical, or supraclavicular adenopathy, nor any skin or nipple changes. Bilateral mammography shows only the index 2-cm right breast lesion, and ultrasound-guided biopsy shows infiltrating ductal cancer with positive estrogen and progesterone receptor expression and absence of *HER2* expression. Options for local therapy could include breast conservation (lumpectomy, sentinel node removal, and radiotherapy) or mastectomy with or without reconstruction. Which factor would be an absolute contraindication to breast conservation therapy?

- A. Patient is 35 weeks pregnant
- B. Previous radiation therapy for a diagnosis of cervical cancer
- C. *BRCA1* mutation carrier
- D. Inability to obtain negative margins of the lumpectomy specimen even after re-excision
- E. Family history of breast cancer in maternal grandmother

Answer: D Randomized clinical trials have demonstrated that breast conservation therapy and mastectomy are equally effective for most women with early-stage breast cancer. Thus, breast conservation therapy is the preferred approach for local therapy for most women. The primary reasons to favor mastectomy include the inability to excise all tumor in the breast (positive margins on re-excision or multifocal breast cancer) or inability to deliver radiotherapy (e.g., during an ongoing pregnancy or after previous mantle radiotherapy for treatment for Hodgkin's lymphoma). In this patient, radiation therapy could be safely delayed for several weeks to permit completion of the pregnancy. Because the breast does not fall in the treatment area for radiotherapy for cervical cancer, this patient could safely receive breast radiotherapy. Family history of breast cancer may contribute to breast cancer risk but does not have an impact on selection of therapy for breast cancer once diagnosed. Breast conservation therapy remains an option for women with a germline *BRCA1* or *BRCA2* mutation, although some patients will opt for bilateral mastectomy. Finally, patient preference should always take precedence after a detailed informed consent discussion has taken place.

2. The patient in Question 1 asks if she should consider genetic testing for a hereditary breast cancer syndrome because of the diagnosis of breast cancer at an early age. What additional element in her history would support the recommendation to proceed with testing?

- A. Personal history of cervical cancer
- B. Patient is of Irish Catholic extraction
- C. Personal history of Hodgkin's lymphoma
- D. Family history of breast cancer in paternal grandmother and ovarian cancer in paternal aunt
- E. Family history of endometrial cancer in mother and postmenopausal breast cancer in maternal grandmother

Answer: D Germline mutations in the *BRCA1* or *BRCA2* gene leading to hereditary breast and ovarian cancer syndromes account for a few percent of breast cancer diagnoses in women. These mutations are autosomal dominant and can thus be inherited through the maternal or paternal line. Careful ascertainment of family history for cancer diagnosis on both sides of the family is critical. Clinical hallmarks of *BRCA1*- or *BRCA2*-related malignancies include the predisposition to breast and/or ovarian cancer (but not endometrial or cervical cancer), bilateral disease, and early onset of disease. Three founder mutations in *BRCA1* or *BRCA2* are found in 1 to 2% of Ashkenazi Jews but have not been described in Irish Catholics.

3. A 70-year-old postmenopausal woman underwent breast conservation surgery and radiotherapy for management of a 1.7-cm, grade 2 infiltrating ductal carcinoma with highly positive estrogen and progesterone receptor and absent *HER2* expression by immunohistochemistry. Sentinel lymph node biopsy was negative. Her general health is good. She takes no medications. Family history is negative for malignancy. A 5-year course of adjuvant treatment with the aromatase inhibitor, anastrozole, is recommended. She should be counseled that a potential side effect of anastrozole is:

- A. Neutropenia.
- B. Arthralgias.
- C. Neuropathy.
- D. Uterine cancer.
- E. Risk of thromboembolic events.

Answer: B Two common types of adjuvant endocrine therapy, tamoxifen and the aromatase inhibitors such as anastrozole, are considered for postmenopausal women with hormone receptor–positive invasive breast cancer. Current guidelines suggest that use of an aromatase inhibitor is preferred for most postmenopausal women. These agents suppress aromatase, the enzyme that converts androgens synthesized in the adrenal glands to estrogens in adipose and breast tissues. Therefore, this patient should be counseled that letrozole could lead to signs and symptoms of estrogen deprivation such as vasomotor symptoms, bone loss, and elevated cholesterol. An increased incidence of arthralgias is also seen in placebo-controlled trials of aromatase inhibitors; the underlying mechanism is not well understood. Because of its estrogen suppressive action, anastrozole administration is not associated with the development of uterine cancer, a malignancy that is associated with unopposed estrogen, nor is it associated with increased risk for thromboembolic events that are seen with tamoxifen or hormone replacement therapy. Finally, unlike cytotoxics, endocrine therapy such as letrozole is not associated with neutropenia or neuropathy.

4. The patient in Question 3 asks what type of breast cancer–specific testing is required during her follow-up in the absence of symptoms. Which is the most appropriate strategy?

- A. Regular history and physical examination without any testing in the absence of symptoms
- B. Regular history and physical examination and annual mammography
- C. Regular history and physical examination and annual mammography and breast MRI
- D. Regular history and physical examination, annual mammography, and routine blood testing, including CBC, chemistry panel, and tumor markers
- E. Regular history and physical examination; annual mammography; routine blood testing including CBC, chemistry panel and tumor markers, and annual PET/CAT

Answer: B Evidence-based guidelines for the follow-up of asymptomatic survivors of early breast cancer recommend regular physical examination and annual mammography. The goal of follow-up in such individuals is to facilitate the early diagnosis of a new breast cancer in the contralateral breast or a recurrence in the ipsilateral breast so that appropriate management can be undertaken. There is no information to support the use of MRI in addition to mammography for this purpose, and bilateral mammography is the preferred approach. A third potential goal is to assess patients for metastatic disease. The primary goal of therapy for metastatic breast cancer is palliation and prevention of symptoms. Randomized trials failed to show a benefit for routine blood tests or whole-body imaging to facilitate this goal or prolong survival. The preferred approach is regular history and physical examination and education of patients about symptoms that might suggest distant recurrence. Breast cancer survivors also should undertake a program of age-appropriate general health measures (e.g., pelvic examination, Pap smear, colon cancer screening, etc.). In addition, a diagnostic evaluation should be undertaken to investigate any suspicious symptoms or findings on physical examination in a survivor of early-stage breast cancer.

5. Multiple hereditary cancer syndromes and their associated genes have been identified. In addition to *BRCA1* and *BRCA2* germline mutations, germline mutations in which gene can predispose to breast cancer?

- A. *p53*
- B. *RET*
- C. *APC*
- D. *VHL*
- E. *HER2*

Answer: A Germline mutations of the *p53* tumor suppressor gene define the Li-Fraumeni hereditary cancer syndrome, which is characterized by predisposition to multiple types of cancer, including breast cancer. Germline mutations of the *RET* gene are associated with multiple endocrine neoplasia (MEN) syndrome 2; its hallmarks are medullary thyroid cancer, pheochromocytoma, and hyperparathyroid gland abnormalities. Inherited mutations of the *APC* tumor suppressor gene characterize familial adenomatous polyposis of the colon and predispose to colon cancer but not breast cancer. Mutated *VHL* is seen in a variety of benign and malignant tumors, including clear cell renal cancers and breast cancer. The *HER2* gene is amplified in 15 to 20% of breast cancers; this somatic change is associated with sensitivity of the tumor to *HER2*-targeted therapy; germline mutations of the *HER2* gene have not been described.

1. Which gynecologic cancer is responsible for the most deaths in the United States each year?

- A. Cervical cancer
- B. Endometrial cancer
- C. Uterine sarcomas
- D. Ovarian cancer
- E. Vulvar cancer

Answer: D As noted in the chapter, endometrial cancer is more than twice as common as ovarian cancer, yet ovarian cancer is more likely to be discovered at an advanced stage. The number of deaths in the United States is roughly twice the number of endometrial cancer deaths. Cervix cancer is much more common in other parts of the world where vaccination and screening are less prevalent.

2. Which of the following women can stop routine cytologic screening for cervical cancer?

- A. A 21-year-old woman immunized at age 19 against HPV
- B. A 38-year-old woman who has completed her childbearing
- C. A *BRCA1* carrier who underwent a risk-reducing salpingo-oophorectomy 5 years ago
- D. A 48-year-old woman who underwent a total hysterectomy for benign uterine bleeding 3 years ago
- E. A 26 year old graduate student with 3 prior negative Pap tests.

Answer: D The immunization for HPV needs to occur before sexual initiation and generally must occur in the early teens at the latest. HPV vaccination has no effect on patients previous infected with HPV. Neither pregnancy nor parity is a major risk factor for cervical cancer, and salpingo-oophorectomy has no benefit for this purpose. However, a woman who underwent a total hysterectomy has no cervical tissue and no risk.

3. Which endometrial cancer stage grouping includes patients most likely to receive a survival benefit from adjuvant whole-pelvic radiation therapy?

- A. Stage IA, grade 1
- B. Stage IB, grade 2
- C. Stage IIIC1, grade 3
- D. Stage IVB, grade 3
- E. Stage IA, grade 3

Answer: C Patients with early-stage (stage I) disease will have decreased local recurrence rates, but no overall survival advantage has been demonstrated to date. A patient with stage III disease with positive pelvic nodes may benefit. Patients with stage IVB will not have disease that can be encompassed in a single field.

4. Which ovarian cancer patient can have postsurgical observation without chemotherapy?

- A. Stage IA, grade 3 serous ovarian cancer
- B. Stage IB, grade 1 serous ovarian cancer
- C. Stage 1C, grade 2 cancer (based on positive peritoneal cytology)
- D. Stage 2A, grade 1 optimally debulked ovarian cancer
- E. Stage IIIA, endometrioid ovarian cancer

Answer: B Only stage IA or IB, grade 1 cancers are suitable for observation.

5. Which of the following is the most common complication of chemoradiation for cervical cancer?

- A. Vascular insufficiency fracture of the pubic ramus
- B. Transitional cell cancer of the bladder
- C. Intermittent diarrhea
- D. Chronic anemia
- E. Rectovaginal fistula

Answer: C Diarrhea can be seen in 10% or more of patients following pelvic radiation. Insufficiency fractures occur less frequently, and radiation-induced tumors are quite rare.

Ch / 200 **TESTICULAR CANCER**

1. A 25-year-old man presents with a mass in his left testis, elevated hCG and α -fetoprotein, 10-cm retroperitoneal mass, and multiple bilateral pulmonary metastases. An orchiectomy revealed embryonal cell carcinoma + teratoma. He is treated with bleomycin + etoposide + cisplatin (BEP) and achieves a complete remission except for a persistent 3-cm retroperitoneal mass. This is subsequently resected and revealed mature teratoma. Seven years later, routine follow-up revealed an elevated serum α -fetoprotein of 150 ng/mL, normal hCG, and normal history and physical examination. His chest CT is normal, but abdominal CT revealed a left-sided pelvic mass measuring 5 cm in size. You now recommend:

- A. Fine-needle aspiration of pelvic mass.
- B. Chemotherapy with paclitaxel + ifosfamide + cisplatin (TIP).
- C. Chemotherapy with vinblastine + ifosfamide + cisplatin (VeIP).
- D. High-dose chemotherapy with peripheral blood stem cell support.
- E. Surgical resection of pelvic mass.

Answer: E This patient has experienced a late relapse. This happens in approximately 2% of patients seemingly cured with initial chemotherapy. Typically, this is first diagnosed during annual follow-up after 5 years from initial chemotherapy and is manifested by an elevated serum AFP and nodal metastasis. The optimal curative strategy is surgery, not salvage chemotherapy.

2. Using the International Staging System for non-seminomatous germ cell tumors, all of the following constitute advanced disease (poor risk) *except*:

- A. Histology of pure choriocarcinoma.
- B. Serum α -fetoprotein greater than 10,000 ng/mL.
- C. Presence of osseous metastases.
- D. Primary mediastinal yolk sac tumor with 8-cm anterior mediastinal mass as only evidence of disease.

Answer: A Histology is not an independent prognostic variable. Any non-pulmonary visceral metastasis, AFP > 10,000 or any primary mediastinal non-seminomatous germ cell tumor constitutes poor-risk disease.

3. A 27-year-old man underwent a left orchiectomy with pathologic findings revealing embryonal cell carcinoma. His pre-orchiectomy serum hCG was 90 MIU/mL and AFP 130 ng/mL. Chest CT was normal, as was physical examination post-orchiectomy. Abdominal CT revealed a 3-cm left para-aortic node. One week later, hCG normalized, but AFP rose to 180 ng/mL. The correct recommendation would be:

- A. Repeat serum AFP 2 weeks later
- B. Fine-needle biopsy of left retroperitoneal lymph node
- C. Three courses of bleomycin + etoposide + cisplatin (BEP)
- D. Four courses of bleomycin + etoposide + cisplatin (BEP)

Answer: C He has a rising serum AFP and requires appropriate chemotherapy for his good-risk metastatic disease with three courses of BEP.

4. Which statement about testicular seminoma is incorrect?

- A. Slight elevation of AFP may be present
- B. Slight elevation of hCG may be present
- C. Most patients present with clinical stage I disease
- D. Radiation therapy is an option for clinical stage II disease with abdominal nodes < 3 cm

Answer: A Most seminomas are clinical stage I. Slight elevations in serum hCG may be observed, but seminomas are never associated with elevated AFP. Radiation therapy remains an option for clinical stage II seminoma.

5. A 35-year-old patient presents with an enlarged left supraclavicular lymph node. An excisional biopsy and complete resection reveals pure seminoma. A testis ultrasound is abnormal, disclosing a small tumor in the right testis. Orchiectomy pathology is also determined to be pure seminoma. Abdominal and pelvic CT scans abnormal with a 2- × 2-cm interaortocaval node. Chest CT is normal. What is the preferred treatment for this patient?

- A. Radiotherapy to abdominal nodes and left supraclavicular fossa
- B. Radiotherapy to abdominal nodes
- C. Retroperitoneal lymph node dissection (RPLND)
- D. Chemotherapy with BEP × 3

Answer: D He has stage III seminoma. The left supraclavicular metastasis was removed, but this is still stage III disease and radiotherapy is inappropriate. RPLND is never an option for initial therapy of any stage of seminoma.

Ch / 201 **PROSTATE CANCER**

1. Which of the following is not a risk factor for prostate cancer?

- A. African American race
- B. Benign prostatic hypertrophy
- C. Obesity
- D. Family history
- E. Dietary factors

Answer: B Neither benign prostatic hypertrophy (BPH) nor a prior history of vasectomy is associated with an increased risk of prostate cancer. The incidence of prostate cancer among African Americans is nearly twice that observed among white Americans. Obesity is associated with several malignancies, and prostate cancer is among the prominent (along with breast cancer, gynecologic malignancies, esophageal adenocarcinoma, colorectal, and renal cell carcinoma). Family history is a significant risk, especially involving relatives of men with early age of onset of prostate cancer. Some dietary factors are likewise considered to enhance or reduce the risk of prostate cancer; the protective nutritional factors include reduced fat intake and increased soy protein (see the Epidemiology section).

2. A 65-year-old man in previously good health generally is found to have an area of induration on the prostate palpable on routine digital rectal examination. The next step should be

- A. prostate biopsy.
- B. PSA level.
- C. imaging for visceral metastases.
- D. cystoscopy.
- E. sigmoidoscopy.

Answer: A Although the digital rectal examination has a low sensitivity and specificity for the diagnosis of prostate cancer, biopsy of a nodule or an area of induration reveals cancer 50% of the time, suggesting that prostate biopsy should be done in all such cases. The PSA (if it has not been already done) will be useful as a parameter of disease to follow if prostate cancer is pathologically diagnosed, but whatever its level is at this time it would not obviate the need for a biopsy. Imaging or procedures to evaluate the local extent of disease or metastases is premature before a pathological diagnosis is made (see the Diagnosis section).

3. Which of the following is effective in preventing prostate cancer?

- A. Vitamin C
- B. Selenium
- C. Nonsteroidal anti-inflammatory drugs (NSAIDs)
- D. Vitamin E
- E. Finasteride

Answer: E Androgen inhibition by the 5 α -reductase inhibitors finasteride and dutasteride has been shown to unambiguously reduce the risk of development of overall prostate cancers, although there was a subsequently disputed finding of an increase in the number of cases with specifically higher grade disease with these drugs. Randomized trials have shown that vitamin C and selenium are not effective in preventing prostate cancer. Vitamin E has not been demonstrated to be effective. NSAIDs have demonstrated effectiveness in prevention of some cancers, such as colorectal cancer, but there is no convincing evidence that its actions likewise apply to the prevention of prostate cancer (see the Prevention section).

Ch / 202

MALIGNANT TUMORS OF BONE, SARCOMAS, AND OTHER SOFT TISSUE NEOPLASMS

1. A 72-year-old woman with metastatic breast cancer to multiple sites who has been treated with an aromatase inhibitor complains of severe left hip pain. Plain radiographs of the pelvis and left femur demonstrate greater than 90% lytic destruction of the femoral neck. Her performance status except for the pain is excellent. The most appropriate therapy, in addition to adequate pain control, to consider at this time is

- A. initiation of combination chemotherapy with doxorubicin and paclitaxel.
- B. intravenous bisphosphonate therapy.
- C. immediate palliative radiation therapy to the left hip.
- D. operative procedure to stabilize the hip.
- E. bed rest followed by reassessment in 6 weeks.

Answer: D Patients with breast cancer at risk of immediate hip fracture should be referred for an orthopedic procedure to stabilize the hip; radiation therapy will follow the surgery, as will consideration of a change in systemic treatment.

2. Which of the following malignancies is associated with germline abnormalities of the *TP53* gene?

- A. Chondrosarcoma
- B. Ewing's sarcoma
- C. Angiosarcoma
- D. Osteogenic sarcoma
- E. Gastrointestinal stromal tumor (GIST)

Answer: D Li-Fraumeni families are characterized by hereditary osteogenic sarcomas that are associated with germline mutations in *TP53*.

3. Gastrointestinal stromal tumors (GISTs) are highly responsive to tyrosine kinase inhibitors that target which of the following proteins?

- A. c-Kit
- B. Epidermal growth factor receptor (EGFR)
- C. BCL-2
- D. Focal adhesion kinase
- E. PDGFRA (platelet-derived growth factor receptor- α)

Answer: A Imatinib, which targets both the c-Kit and bcr-abl kinase, is highly active in the treatment of GISTs (as well as chronic myelogenous leukemia).

4. Which of the following statements concerning soft tissue sarcomas is **incorrect**?

- A. Soft tissue sarcomas are a relatively homogeneous group of malignancies at the molecular level because they all originate from primordial mesenchyme.
- B. Classification of soft tissue sarcoma subtypes is difficult at the level of light microscopy.
- C. Traditional cytotoxic chemotherapy is only useful for specific types of soft tissue sarcoma.
- D. Radiation to the chest wall as part of a combined modality approach to patients with breast cancer can lead to secondary sarcomas in the radiated field.
- E. Many benign tumors (e.g., lipomas) cannot be easily distinguished clinically from frankly malignant sarcomas.

Answer: A Soft tissue sarcomas are among the most heterogeneous groups of malignancies currently known.

5. Which of the following sarcomas has the best prognosis after definitive surgery?

- A. Ewing's sarcoma
- B. Liposarcoma
- C. Chondrosarcoma
- D. Leiomyosarcoma
- E. Osteosarcoma

Answer: C Definitive surgery is curative in many patients with chondrosarcoma; the recurrence rate after surgery with each of the other diseases is considerably higher.

1. A 62-year-old woman was recently diagnosed with a 0.77-mm-thick melanoma. There was no ulceration, it was a Clark's level III, and the mitotic count was 1.0/mm². The melanoma arose from her left posterior arm. The patient had blood work performed, which included a CBC, chemistry panel, and LDH, which were normal. Which of the following imaging studies is appropriate for this patient?

- A. No imaging studies
- B. CT scan of the chest, abdomen, and pelvis and MRI of the brain
- C. PET/CT scan and MRI of the brain
- D. Bone scan; CT scan of the chest, abdomen, and pelvis; and brain MRI
- E. CT scan of the chest, abdomen, and pelvis

Answer: A The staging evaluation of a patient with a low risk melanoma should include a physical examination, including a skin examination. Routine blood work and imaging is not routinely recommended. The majority of patients who present with melanoma do not have distant metastatic disease at presentation; therefore, extensive evaluations with computed tomography (CT) scans to search for distant metastases have an extremely low yield and consequently are not indicated in asymptomatic patients. More extensive staging evaluation with CT scans of the chest, abdomen, and pelvis can be considered in patients with high-risk disease (thick primary melanoma >4 mm thick or node-positive disease) in whom the risk of distant metastatic disease is higher.

National Comprehensive Cancer Network (NCCN) guidelines. Available at <http://www.nccn.org>.

2. A 55-year-old man presents to your office with a right axillary lump. Two years ago, he was treated for a malignant melanoma on his right upper arm. The melanoma was 1.3 mm thick, and there was no ulceration present. The melanoma was treated with wide excision, which showed no residual melanoma, and the patient was then monitored. He now presents to your office with an enlarged right axillary lymph node, which measures 2.5 × 2.0 cm. The patient has no symptoms, no fever, and the remainder of the physical examination findings are unremarkable. Which of following would you recommend to this patient now?

- A. Arrange for fine-needle aspiration (FNA) of the lymph node
- B. Surgical excision of the lymph node
- C. Prescribe of a 10-day course of antibiotics
- D. Referral to radiation therapy to begin radiation therapy to right axillary region
- E. Continue monitoring and have the patient return to the office in 3 months because this likely represents a postoperative seroma

Answer: A In this patient with a history of melanoma, an enlarged regional lymph node is highly suspicious for disease recurrence. Obtaining an FNA, often with ultrasound guidance, is the most appropriate next step to confirm diagnosis. The physical examination does not suggest this represents an infection, and postoperative seroma would be highly unusual this far out from surgery. After melanoma is confirmed, then staging evaluation should be completed with CT scans of the chest, abdomen, and pelvis or PET scan. Additional surgery with complete lymph node dissection and plans for adjuvant systemic therapy would follow providing no distant metastatic disease was identified.

3. A 35-year-old woman presents with a mild cough, fatigue, and some weight loss. She was treated for melanoma on her left lower leg 3 years ago. Imaging studies reveal multiple pulmonary nodules. A CT-guided biopsy confirms diagnosis of metastatic melanoma. Analysis of the tumor for which of the following mutations would be most useful in determining treatment options?

- A. *KIT*
- B. *BRAF*
- C. *EGFR*
- D. *ALK*
- E. *KRAS*

Answer: B *BRAF* V600 is the most common somatic mutation in melanoma, occurring in 50% of patients. It also tends to occur in younger patients with melanoma, so this is the most likely mutation in this patient. Importantly, *BRAF* inhibitors (vemurafenib, dabrafenib) are effective therapies for patients with *BRAF* mutant melanoma and are now approved by the Food and Drug Administration based on survival benefit demonstrated in randomized phase III clinical trials. *KIT* is uncommonly mutated in melanoma (<3% of melanomas). *KIT* mutations are most frequent in acral (arising on palms and soles or subungual), mucosal melanoma or cutaneous melanomas associated with chronic sun exposure. In this patient, testing for *BRAF* mutation first is most appropriate. *EGFR* mutation is not associated with melanoma; it is mutated in lung cancer. *ALK* and *KRAS* are not somatic mutations that occur in melanoma.

4. Which of the following patients has the highest risk for developing melanoma?

- A. A 35-year-old woman with red hair and blue eyes who has had more than five blistering sunburns
- B. A 72-year-old farmer who has had chronic sun exposure for more than 60 years
- C. A 68-year-old woman who has had several basal cell and squamous cell skin cancers
- D. A 29-year-old woman with multiple dysplastic nevi and an uncle and cousin who had melanoma

Answer: D All of these patients are at increased risk for melanoma. Individuals with red hair, blue eyes, history of blistering sun burns, chronic sun exposure, and history of nonmelanoma skin cancers (basal cell and squamous cell) are at increased risk. However, the highest risk patient is the woman with dysplastic nevi and a family history of melanoma. In this patient, a careful family history should be obtained to determine if additional relatives have melanoma or other cancers, and all should be referred for dermatology evaluation. This patient could be part of familial melanoma/dysplastic nevus syndrome, which is associated with very high risk of developing melanoma and associated with germline mutation in *p16*.

5. A 44-year-old man was recently diagnosed with stage IV melanoma. Staging workup showed multiple liver metastases, lung metastases, and bone metastases. Symptoms at this time include mild shortness of breath, cough, significant bone pain, and an 8-lb weight loss. Mutation testing for *BRAF* confirmed V600E *BRAF* mutation. What treatment would you recommend now?

- A. Dabrafenib
- B. Trametinib
- C. Imatinib
- D. Sorafenib

Answer: A In this patient with symptomatic metastatic melanoma, the most appropriate choice would be a highly potent and selective *BRAF* inhibitor. Dabrafenib treatment is associated with an approximately 60% response rate. Clinical benefit has been seen within 72 hours of administration. Trametinib is a recently approved MEK inhibitor; however, clinical activity is less than that reported for dabrafenib. Similarly, sorafenib, although it targets *BRAF*, has little activity in melanoma. Imatinib targets *c-kit*, so its selection is not appropriate.

Ascierto P, Minor D, Ribas A, et al. Phase II trial (BREAK-2) of the *BRAF* inhibitor dabrafenib (GSK118436) in patients with metastatic melanoma. *J Clin Oncol*. 2013;31:3205-3211.

6. A 63-year-old woman was recently diagnosed with stage IV melanoma. Staging workup showed lung and bone metastases. She has no symptoms at this time. Her oncologist has recommended treatment with ipilimumab. Which of the following statements best describes the mechanism of action of ipilimumab?

- A. Blocks cytotoxic T-lymphocyte antigen 4 (CTLA-4)
- B. Inhibits DNA replication
- C. Inhibits the MAP kinase pathway
- D. Directly stimulates T cells activity
- E. Interferes with CD 20 on B cells

Answer: A Ipilimumab is a negative regulator of T-cell activation. It interferes with the ability of CTLA-4 to interact with its ligand, which is an inhibitory signal. Thus, CTLA-4 blockade with ipilimumab results in T-cell activation and proliferation. Ipilimumab, a type of immunotherapy, is approved by the Food and Drug Administration (FDA) for the treatment of unresectable stage III and IV melanoma. Chemotherapy agents such as cyclophosphamide interfere with DNA replication. Molecularly targeted agents such as BRAF inhibitors work through inhibiting the MAP kinase pathway. Interleukin-2, FDA approved for the treatment of metastatic melanoma, directly stimulates T cells. Monoclonal antibodies, such as rituximab, induces destruction of B cells, which express CD 20. This therapy is used to treat patients with chronic lymphocytic leukemia and non-Hodgkin's lymphoma.

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CANCER OF UNKNOWN PRIMARY ORIGIN

1. A 65-year-old man, former cigarette smoker, presents with an asymptomatic right neck mass. He feels well otherwise. Physical examination is normal except for a firm, nontender, movable 2 cm lymph node in the right jugulodigastric area. CT scan of the neck shows the palpable right cervical node and two adjacent nodes, each measuring 1.5 cm, deeper in the right anterior cervical area. CT scans of the chest and abdomen are normal. Needle biopsy of the palpable node shows squamous carcinoma. The most likely diagnosis is

- A. metastatic lung cancer.
- B. metastatic gastric cancer.
- C. locally advanced base of tongue cancer.
- D. metastatic esophageal cancer.
- E. metastatic squamous skin cancer.

Answer: C Squamous cell carcinomas (SCCs) arising from various sites in the head and neck (nasopharynx, oropharynx, hypopharynx, larynx) frequently metastasize to ipsilateral upper cervical lymph nodes. In 85% of patients who present with metastatic SCC in the upper cervical nodes, appropriate evaluation identifies the head or neck primary site. SCCs of the lung or esophagus occasionally present with a palpable neck node but almost always in the lower cervical or supraclavicular area. Metastatic gastric cancer sometimes spreads to the left supraclavicular nodes (Virchow's nodes) but has adenocarcinoma histology. Metastases from SCC skin cancers are rare.

2. In the patient described in question 1, the procedure most likely to identify the primary site is

- A. PET scan.
- B. ENT endoscopy (nasopharynx, oropharynx, hypopharynx, larynx).
- C. fiberoptic bronchoscopy.
- D. upper GI endoscopy.
- E. right radical neck dissection.

Answer: B Endoscopy with visualization of the mucosal surfaces of the nasopharynx, oropharynx, hypopharynx, and larynx identifies a primary site in a large majority of such patients. PET scan can also identify an occult head or neck primary site but much less consistently. Bronchoscopy and upper GI endoscopy are not usually productive because most often the primary site is in the head or neck. Radical neck dissection before further evaluation is inappropriate.

3. A previously healthy 30-year-old man presents with fatigue, a 10-lb weight loss, and severe abdominal and back pain that has steadily increased during the past month. Abdominal CT scan shows a 15 × 10 × 8 retroperitoneal mass, with the superior aspect adjacent to the pancreas but not clearly invading the pancreas or other organs. A CT-guided core needle biopsy shows poorly differentiated

carcinoma. A chest CT scan shows a single 0.5-cm noncalcified right lung nodule of questionable significance. Further evaluation should include all of the following except

- A. immunohistochemical staining of the biopsy specimen (by pathologist) to better characterize the cancer type.
- B. GU history, particularly any history of cryptorchidism.
- C. testicular ultrasonography.
- D. serum hCG and AFP levels.
- E. endoscopic retrograde cholangiopancreatography (ERCP).

Answer: E Because of this patient's age, tumor location in the retroperitoneum, and biopsy showing poorly differentiated carcinoma, an extragonadal germ cell tumor (EGCT) is a likely diagnosis and is definitely the most treatable carcinoma in this setting. Additional pathologic evaluation with immunohistochemical stains (OCT4, PLAP, hCG) may support a germ cell tumor diagnosis, and high-grade non-Hodgkin's lymphoma (occasionally mistaken for a poorly differentiated carcinoma) should be ruled out with an LCA stain. Elevated serum hCG or AFP in this clinical setting would provide strong evidence for an EGCT. The risk of germ cell tumor is increased in patient with cryptorchidism even after surgical correction. Pancreatic cancer is an unlikely diagnosis in this situation (size and location of mass, age of patient, histology), and ERCP would prolong the evaluation and delay initiation of treatment.

4. A 60-year-old woman presents with a 2-month history of anorexia, 15-lb weight loss, and mild RUQ abdominal discomfort. Physical examination results are normal. Blood counts are normal; the chemistry profile reveals levels of AST and ALT three times the upper limit of normal. Abdominal CT scan shows six liver lesions consistent with metastases (the largest is 4 cm). Chest CT scan is normal. Colonoscopy is normal. Liver biopsy (core needle) shows metastatic adenocarcinoma compatible with a GI primary tumor; immunohistochemical staining shows CK20 positive, CK7 negative, and CDX2 positive. Molecular tumor profile predicts a colorectal site of tumor origin. Best management includes

- A. treat with chemotherapy for metastatic colon cancer.
- B. repeat the colonoscopy.
- C. laparotomy to search for primary site and resect liver metastases if possible.
- D. treat with empiric chemotherapy for cancer of unknown primary site.
- E. advise the patient that treatment in this situation will probably be ineffective and discuss hospice referral.

Answer: A This patient has a carcinoma of unknown primary site with a colon cancer "profile": metastases to liver, typical adenocarcinoma histology, and suggestive immunohistochemical staining. In addition, the molecular tumor profiling prediction is colon cancer. Site-specific treatment of metastatic colon cancer is currently associated with median survival time of 20 to 24 months, which is substantially better than the expected 9- to 11-month median survival time with empiric CUP chemotherapy and long enough that hospice referral is not appropriate. A negative colonoscopy is frequent in patients with this syndrome; repeat colonoscopy will not change treatment, even if a small primary colon cancer is found. Resection of six liver metastases is very unlikely to be beneficial even if technically feasible. However, resection of residual hepatic metastases may have a role in patients who have an excellent response to first-line chemotherapy.

5. A 45-year-old premenopausal woman presents with a new mass in her right groin. She feels well and denies any recent urinary or gynecologic symptoms. Physical examination reveals a firm, nontender 2.5-cm right inguinal lymph node, with an adjacent 1.5-cm node, also firm and nontender. CT scans of the chest, abdomen, and pelvis reveal no additional findings. A needle biopsy of the largest inguinal lymph node shows metastatic squamous cell cancer. In this patient, procedures indicated in a search for the primary site may include all except

- A. pelvic examination with colposcopy and biopsy of suspicious lesions.
- B. cystoscopy.

- C. PET scan.
- D. breast MRI.
- E. anoscopy.

Answer: D Female patients who present with squamous cell cancer metastatic to inguinal nodes usually have a primary site that is detectable in the vagina, cervix, bladder, or anorectal area. Evaluation should search for these primary sites. If metastases from any of these primary sites are limited to ipsilateral inguinal lymph nodes, appropriate treatment is sometimes curative. This presentation (location of metastases, squamous histology) is not suggestive of breast cancer, and a breast MRI is an unnecessary procedure in this situation.

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APPROACH TO INBORN ERRORS OF METABOLISM

1. Which of the following statements is correct regarding disorders caused by inborn errors of metabolism?
 - A. They present clinically in neonates and early childhood because the metabolic pathways disrupted in these disorders affect vital organ functions.
 - B. They are typically autosomal recessive diseases caused by founder mutations and parental consanguinity.
 - C. They can affect multiple organs with the exception of the central and peripheral nervous systems.
 - D. They may present with pathognomonic clinical signs.
 - E. They are characterized by mitochondrial inheritance.

Answer: D Inborn errors of metabolism may exhibit clinical signs that are diagnostically pathognomonic, such as ochronosis and black urine in alkaptonuria or angiokeratomas and cornea verticillata in Fabry's disease (see Table 205-4). The clinical phenotypes of inborn errors of metabolism range widely from severe disease presenting in infancy to mild symptoms and signs recognized only in adulthood as well as many cases that are asymptomatic and consistent with normal life expectancy. They are monogenic conditions that follow autosomal recessive or dominant, X-linked recessive or dominant, or mitochondrial inheritance patterns. More than 50% of clinical overt cases affect the central or peripheral nervous system. (See section on pathobiology.)

2. Which of the following therapeutic modalities is *not* currently in use for the clinical management of patients with inborn errors of metabolism?
 - A. Intravenous enzyme replacement therapy
 - B. Stem cell therapy
 - C. Liver transplantation
 - D. Nutritional therapy
 - E. None of the above has been shown to be effective in any inborn errors of metabolism.

Answer: B Examples of effective treatments include intravenous enzyme (glucocerebrosidase) replacement therapy (A) for Gaucher's disease; liver transplantation (C) for tyrosinemia type I, urea cycle defects, methylmalonic aciduria, propionic aciduria, lysosomal lipase deficiency, and glycogen storage diseases; and nutritional therapy (D) for phenylketonuria by reduction in phenylalanine intake through low-protein food along with simultaneous supplementation with phenylalanine-free amino acids. Stem cell therapy is currently under investigation for glycogen storage disease type I. (See section on treatment.)

3. Which of the following is *not* currently considered first-line diagnostic testing for inborn errors of metabolism?

- A. Whole exome sequencing
- B. Biochemical analysis of metabolites in body fluids
- C. Enzyme testing in tissues
- D. Tissue biopsies for histology and histochemistry
- E. Prenatal and carrier testing

Answer: A Most inborn errors of metabolism can be diagnosed by analysis of small-molecule metabolites in appropriate body fluids like whole blood, serum, urine, and cerebrospinal fluid (B). This is usually followed by appropriate enzyme testing in tissues like dried whole blood, leukocytes, fibroblasts, and muscle tissue (C). Tissue biopsies for histology and histochemistry (D) are still of value in some cases. Molecular confirmation is available for prediction of phenotype and is a prerequisite for family planning, including preimplantation diagnosis, prenatal testing, and carrier testing for the partner (E). Clinical whole genome or exome sequencing in CLIA- and CAP-accredited laboratories may aid in the diagnosis of rare mendelian disorders like inborn errors of metabolism, but analytical challenges remain and should be considered at this time only if all other diagnostic avenues are exhausted. (See section on diagnosis.)

4. A 35-year-old woman is brought to the emergency department with a history of acute-onset nausea, headaches, and stupor after a protein-rich meal. She has a history of similar events in the past. Her brother died as an infant of an encephalopathic crisis. The plasma ammonium level on admission is 400 $\mu\text{mol/L}$ (reference: $<40 \mu\text{mol/L}$). What is the most appropriate initial treatment?

- A. Enzyme replacement therapy
- B. Liver transplantation
- C. Intravenous fluids only
- D. Alternative pathway therapy with intravenous sodium benzoate or sodium phenylbutyrate
- E. Hydroxycobalamin IM

Answer: D The 35-year-old woman suffers from ornithine transcarbamylase (OTC) deficiency. OTC is a urea cycle enzyme that is part of the urea cycle responsible for conversion of nitrogen to urea. Deficiency of any of the five urea cycle enzymes and three transporter proteins will lead to variable elevations of plasma ammonium during episodes of intercurrent illnesses, catabolism, or high-protein meals. OTC deficiency is inherited as an X-linked recessive trait, explaining why the affected brother died as an infant during a hyperammonemic crisis. Female carriers of OTC deficiency may show symptoms only when they are exposed to a high-protein meal. The goal of therapy is to normalize ammonium levels quickly through alternative pathway therapy, hemofiltration, or hemodialysis. Outcome is poor if ammonium levels are not corrected in a timely manner.

5. A 32-year-old man from Pakistan with a seizure disorder has been recently diagnosed with an inborn error of metabolism. His family history is remarkable for an affected sister and consanguinity of the healthy parents. There is a distant male cousin with the same condition. Given this family history, what is the most likely mode of inheritance for this condition?

- A. Mitochondrial inheritance
- B. X-linked recessive inheritance
- C. Autosomal recessive inheritance
- D. Autosomal dominant inheritance with complete penetrance
- E. Complex inheritance including different genetic and environmental factors

Answer: C Due to consanguinity of the healthy parents and absence of affected family members in other generations, autosomal recessive inheritance is the most likely mode of inheritance for the condition in question. Mitochondrial (maternal) inheritance of mutations in mitochondrial genes may be observed in respiratory chain disorders, with variable expressivity of disease due to heteroplasmy. X-linked recessive inheritance as in OTC deficiency results in severely affected males and mildly or

unaffected carrier females. Disorders with an autosomal dominant inheritance with complete penetrance affect multiple family members at each generation. The recurrence risk is 50% for future offspring of affected individuals. Complex inheritance may be observed in cancer, glaucoma, and Alzheimer's disease because of different contributions from genetic and environmental factors.

6. A 23-year-old woman and her 25-year-old husband, both of Ashkenazi Jewish ancestry, are seen for genetic counseling regarding their risk of having a child with Gaucher's disease or other conditions. What is the most appropriate response regarding their risk?

- A. Their risk of having a child with Gaucher's disease is negligible.
- B. Carrier screening of both parents for Gaucher's disease through analysis of common mutations in the *GBA* gene is indicated.
- C. Prenatal diagnosis is recommended during early pregnancy through analysis of glucocerebrosidase activity in amniocytes.
- D. Carrier screening of both parents should be comprehensive and include an Ashkenazi Jewish disease panel and SMA (spinal muscular atrophy) for both parents and fragile X for the mother.
- E. Only karyotyping for the mother is indicated.

Answer: D The carrier frequency for a number of genetic conditions including Gaucher's disease is markedly increased in individuals of Ashkenazi Jewish ancestry. Carrier screening should therefore not be restricted to Gaucher's disease but also include Tay-Sachs disease, Canavan's disease, spinal muscular atrophy, and many others for both parents as well as fragile X for the mother.

7. A 19-year-old man has been diagnosed with a disorder of fatty acid oxidation. He is at increased risk for complications due to which pathophysiologic mechanism?

- A. Accumulation of toxic substrates due to blockage of pathway
- B. Energy failure due to primary blockage of a pathway that is important for ATP synthesis
- C. Progressive accumulation of nontoxic substrates due to a defect in a catabolic pathway
- D. Defect in post-translational glycosylation
- E. Blockage of an anabolic pathway

Answer: B Disorders of fatty acid oxidation lead to reduced β -oxidation of fatty acids of various chain lengths, depending on the exact enzyme deficiency. As a consequence, fewer acetyl-CoA equivalents are produced that would be available for ATP or ketone body synthesis. Clinically, patients with disorders of fatty acid oxidation have a reduced fasting tolerance and are at risk for hypoglycemia and energy failure in skeletal and cardiac muscles.

8. The diagnosis of a mucopolysaccharidosis type I is suspected in a 21-year-old woman with hepatosplenomegaly, corneal clouding, and carpal tunnel syndrome. What is the first-line diagnostic test to confirm the diagnosis?

- A. Urine glycosaminoglycans
- B. Urine organic acids
- C. Plasma acylcarnitine profile
- D. Plasma amino acids
- E. Whole exome sequencing

Answer: A Mucopolysaccharidosis type I is characterized through increased excretion of dermatan and heparan sulfates (glycosaminoglycans).

1. A 46-year-old man presents with hypercholesterolemia. He underwent coronary artery bypass grafting at the age of 43 years. He has a 20 pack-year history of smoking but quit tobacco after his bypass surgery. His father died suddenly of unknown causes at the age of 45 years, and an older brother had a myocardial infarction in his 50s. The patient is currently taking amlodipine, metoprolol, and aspirin. He took some type of statin in the past but did not like the way it made him feel. His examination is notable for a body mass index of 25, blood pressure of 150/92 mm Hg, arcus corneae, a fourth heart sound on cardiac examination, no evidence of heart failure, and thickened Achilles tendons. His laboratory results are notable for normal renal and liver function, normal fasting glucose concentration, total cholesterol level of 290 mg/dL, low-density lipoprotein (LDL) level of 232 mg/dL, high-density lipoprotein (HDL) level of 44 mg/dL, and triglyceride level of 135 mg/dL. Which course of action might be appropriate?

- A. Noninvasive imaging to assess the status of his bypass grafts before deciding on a medical regimen.
- B. Referral to a dietitian (with a goal of decreasing dietary cholesterol and saturated fat) and initiation of statin therapy with rapid escalation to maximum recommended doses.
- C. Initiation of fibrate therapy, given his apparent intolerance of a statin.
- D. Referral to a dietitian, optimization of blood pressure control, and gradual introduction of a statin in combination with one or more additional agents for LDL lowering.

Answer: D This patient has heterozygous familial hypercholesterolemia, caused by the presence of a single copy of a deficient allele for the LDL receptor. Whereas the development of atherosclerosis can vary in familial hypercholesterolemia, this individual is known to have vascular disease, and imaging will be unlikely to affect his lipid management. Dietary advice is warranted, but a statin alone or a fibrate alone will be inadequate for LDL lowering. Therapeutic lifestyle changes, management of other risk factors for atherosclerosis (such as hypertension), and initiation of lipid therapy that includes a statin as well as agents with complementary mechanisms of action (such as a bile acid sequestrant and niacin) are most appropriate.

2. A 39-year-old man is referred for management of high cholesterol. He was recently hospitalized for uncontrolled diabetes and severe abdominal pain. Review of the electronic medical record from that admission revealed no previous history of diabetes, peak glucose concentration of 390 mg/dL, no evidence of diabetic ketoacidosis, pancreatitis detected on abdominal computed tomography scanning, initial total cholesterol level of 945 mg/dL, triglyceride level of 4732 mg/dL, and hemoglobin A1c level of 10.5%. He was made NPO, was treated with insulin, and improved during several days. He was discharged with a total cholesterol level of 371 mg/dL and triglyceride level of 947 mg/dL, with a laboratory notation that the sample was lipemic. His discharge medications included a high dose of rosuvastatin, long-acting insulin, and metformin. Which of the following statement(s) about this presentation is (are) true?

- A. The elevated total cholesterol level in this patient indicates a very high risk of cardiovascular disease.
- B. Skin lesions, transient hepatosplenomegaly, mild cognitive impairment, and abnormal eye findings are associated with this condition.
- C. Elevated triglycerides in this condition should be treated with plasmapheresis.
- D. Appropriate therapy may result in nearly normal lipid levels in this patient.

Answers: B and D This patient has the chylomicronemia syndrome, usually due to a genetic predisposition to hypertriglyceridemia in combination with uncontrolled diabetes. These patients may have xanthomas (especially on the trunk), organomegaly, confusion, and lipemia retinalis on funduscopic examination. The presence of chylomicrons is suggested by the laboratory detection of lipemia. The very high levels of cholesterol probably do not indicate a high risk of vascular disease because they reflect the presence of chylomicrons that are thought to be too large to enter the vascular wall. Pheresis is not usually indicated. Potent statins such as rosuvastatin are not appropriate initial therapy. Optimized glycemic control and some combination of a fibrate, niacin, and fish oils are indicated to maintain fasting triglyceride levels below 500 mg/dL, a value thought to be associated with less risk of lipid-induced pancreatitis. Many of these patients are obese, and significant weight loss can result in near-normalization of lipid levels.

3. A 44-year-old woman presents with elevated triglycerides. Except for childbirth, she has never been hospitalized. She admits to being sedentary but wants to lose weight. She denies chest pain or other symptoms. She has had abnormal lipids for several years and previously tried niacin but could not tolerate the side effect of flushing. She does not drink alcohol or use tobacco and takes no medications except for ibuprofen for menstrual cramps. Her father died at the age of 58 years, around the time of an elective surgical procedure. She has three sisters, and all have elevated triglycerides, although none is known to have heart disease. There is no family history of pancreatitis. Her examination findings are normal except for a body mass index of 34. Her fasting lipids are notable for triglyceride level of 318 mg/dL, total cholesterol level of 243 mg/dL, LDL cholesterol level of 126 mg/dL, and HDL cholesterol level of 34 mg/dL. Appropriate management could include which of the following?

- A. Noninvasive imaging to assess the possibility of coronary artery disease.
- B. Therapeutic lifestyle changes for 6 months followed by fibrate therapy, given her intolerance of niacin by history.
- C. Therapeutic lifestyle changes for 6 months followed by initiation of prescription fish oil therapy at low doses with gradual escalation to the maximum recommended dose.
- D. Therapeutic lifestyle changes and initiation of statin therapy at this visit.

Answer: D This patient has familial combined hyperlipidemia, perhaps the most common inherited lipid disorder. It is associated with premature coronary disease. She has no symptoms, so noninvasive cardiac imaging may not be useful, but a treadmill stress test might be helpful as she considers starting an exercise program as part of therapeutic lifestyle changes. Statin therapy should be recommended. Whereas her LDL level is not particularly high, her non-HDL cholesterol level is 209 mg/dL. An appropriate goal might be a non-HDL cholesterol level of less than 130 mg/dL.

4. A 67-year-old man presents to you with statin intolerance. He underwent coronary artery bypass grafting at the age of 55 years and has taken simvastatin followed by atorvastatin for many years with no symptoms. Recent angiography demonstrated patent grafts. Several months ago, he developed vague aching and cramping in his lower extremities that was attributed to his statin. His atorvastatin was discontinued and the symptoms improved, but they did not resolve. Other statins were prescribed, and all were associated with increased muscle cramping, especially noticed at night. He has now been off statins for a month and currently complains of muscle pain, constipation, and recent weight gain of about 10 pounds that he attributes to physical inactivity due to muscle pain. His examination is notable for a blood pressure of 142/94 mm Hg with two antihypertensives, pulse of 58, periorbital edema, no evidence of heart failure, mild diffuse muscle tenderness without fasciculations, and trace lower extremity edema. His laboratory results reveal an LDL cholesterol level of 157 mg/dL and a creatine kinase level of 351 µg/L (normal, <120 µg/L). What is the best next step for this patient?

- A. Admission to the hospital for management of rhabdomyolysis
- B. Muscle biopsy
- C. Initiation of ezetimibe to lower LDL cholesterol
- D. Assessment of renal and thyroid function

Answer: D This patient has hypothyroidism. He does not have rhabdomyolysis, which is associated with extreme elevations of muscle enzymes, severe muscle pain, dark urine, and renal dysfunction. A muscle biopsy is not indicated at this point. Ezetimibe might be a useful adjunct, but its use does not address his muscle symptoms. The current level of creatine kinase elevation is modest, but it is prudent to assess renal function because this patient may have had greater degrees of muscle dysfunction while taking statins. In this patient, thyroid-stimulating hormone was elevated and free thyroxine was decreased, consistent with primary hypothyroidism. This condition is common, increases the risk for statin-induced myopathy, and causes myopathy independent of statins. Once thyroid status is corrected with thyroid hormone, statin therapy, reintroduced cautiously, can be well tolerated.

5. A 56-year-old woman with type 2 diabetes presents to your office for routine care. She is postmenopausal and has intermittent vasomotor symptoms but does not wish to take estrogens because of concerns about side effects. She smoked less than a pack of cigarettes a day in her 20s but quit more than 20 years ago. Her most recent hemoglobin A1c level is 7.4%, she does not have microalbuminuria, and there is no personal history of heart disease, but both of her parents died of cardiovascular causes after the age of 65 years. She has no complaints except for knee pain due to osteoarthritis. Her current medications include losartan, exenatide, and metformin. Except for a body mass index of 29, her examination findings are normal. Her most recent lipid panel is notable for triglyceride level of 145 mg/dL, HDL level of 50 mg/dL, and LDL level of 96 mg/dL. She realizes that cardiovascular disease is the most common cause of death in diabetes but does not wish to take statins because her LDL is already below 100 mg/dL and she is wary of statins, especially since they are reported to cause diabetes. Which of the following represents appropriate advice for this patient?
- A. Begin statin therapy with a goal of decreasing LDL by 30 to 40% from the current level of 96.
 - B. Begin insulin therapy with a goal of lowering the hemoglobin A1c to a nearly normal level.
 - C. Institute an aggressive program of weight loss through diet and exercise to decrease the risk of cardiovascular disease.
 - D. Begin nutritional supplements including chromium, antioxidant vitamins, and low-dose fish oils.

Answer: A Even if lipid levels are initially fairly low, patients at risk for coronary disease, like this woman with diabetes, benefit from statin treatment. Aggressive attempts to improve glycemia in this population of patients do not clearly provide benefit and may cause harm. A controlled trial of weight loss did not decrease cardiovascular events in subjects similar to this patient. Supplements including minerals, vitamins, and fish oils have not been shown to provide cardiovascular benefit in individuals like this patient.

Ch / 207 **GLYCOGEN STORAGE DISEASES**

1. Which of the following symptoms and signs would *not* be a likely presenting manifestation of glycogen storage disease in an adult?
- A. Unexplained hepatomegaly
 - B. Limb-girdle muscle weakness
 - C. Transient ischemic attacks
 - D. Symptoms of hypoglycemia
 - E. Muscle cramps

Answer: C Most cases of glycogen storage disease seen by internists will have been already diagnosed in childhood. However, individuals with much milder disease (presumably associated with less severe enzyme activity as determined by genotype) may present with symptoms and signs in adulthood. Hepatomegaly (A) and hypoglycemia (D) are the principal clinical manifestations of the hepatic glycogenoses; muscle cramps (E), exercise intolerance, and progressive fatigue and weakness are the major manifestations of the muscle glycogenoses (see Table 207-1). For example, whereas infants with Pompe's disease (type II glycogen storage disease) present at birth (floppy infant syndrome) or shortly thereafter and progress to respiratory failure, cardiomyopathy, and death by the age of 1 year unless treated, adult-onset disease commonly is manifested as limb-girdle muscle weakness (B), which can mimic that of other musculoskeletal disorders, especially muscular dystrophies. (Vissing J, Lukacs Z, Straub V. Diagnosis of Pompe disease. *JAMA Neurol*. 2013;70:923-927.) Cerebrovascular disease (C) may be seen in homocystinuria but is not known to be associated with glycogen storage diseases.

1. All except which of the following are different defects that can result in lysosomal storage disorders?

- A. Sphingolipidosis
- B. Lysosomal transport disorders
- C. Phenylketonuria
- D. Oligosaccharidoses
- E. Lipid storage disorders

Answer: C Lysosomal storage disorders are a group of more than 45 different inherited disorders, all sharing a defect in lysosomal function. Lysosomes, acidic, membrane-bound organelles present in the cytoplasm, contain enzymes that degrade cellular macromolecules. These disorders occur when one or more of the hydrolytic enzymes are deficient or when essential lysosomal transporters, receptors, cofactors, or protective proteins are defective or lacking. Sphingolipidosis, the oligosaccharidoses, lipid storage disorders, and lysosomal transport disorders are all considered lysosomal storage disorders. Phenylketonuria is a disorder of amino acid metabolism, and abnormal lysosomal storage does not occur.

2. To make the diagnosis of a lysosomal storage disorder:

- A. A tissue biopsy is often necessary.
- B. DNA analyses are required.
- C. Enzymatic assays can be performed on a blood or fibroblast sample.
- D. Urine tests are the standard of care.
- E. Clinical criteria alone are adequate.

Answer: C The diagnosis of most lysosomal storage disorders can be made by assaying the enzyme activity in a blood sample or fibroblasts pellet from a skin biopsy specimen. The first tier of diagnostics should be a lysosomal disease diagnostic panel, evaluating the enzyme activity of multiple lysosomal enzymes. Whereas the genes encoding the lysosomal enzymes have been identified and mutation analysis is available, there is vast genotypic heterogeneity. Thus, mutation screening is most useful when a mutation has already been identified in a specific family or when specific mutations are known to be common in an ethnic group.

3. A 24-year-old woman with no prior health issues presents with sudden onset of dysarthria and right hemiparesis. She also mentions that she “sweats less than her peers during exercise.” She had a paternal grandmother and uncle who both died of renal disease in their fourth decade. Her work-up should include testing for:

- A. Gaucher disease
- B. Fabry disease
- C. Glycogen storage disease
- D. Wolman’s disease
- E. All of the above

Answer: B Female carriers of Fabry disease, which is an X-linked disorder, have less severe symptoms with a later age at onset. About 40% of affected women have stroke as the initial symptom. Whereas the typical skin finding in Fabry disease of angiokeratoma is not seen in women, about half complain of hypohidrosis and heat intolerance. Renal involvement is common, with progressive renal insufficiency and end-stage renal disease in the second to fourth decades. Affected men have proteinuria, which is less frequently seen in affected women, even those affected with renal disease. Gaucher disease, glycogen storage disease, and Wolman’s disease are not manifested with stroke symptoms in men or women.

4. A 22-year-old Ashkenazi Jewish college student presents with thrombocytopenia and painless splenomegaly. He is otherwise healthy with no relevant family history. His work-up should include diagnostic testing for

- A. Hurler's disease
- B. Fucosidosis
- C. Cystinosis
- D. Gaucher disease
- E. Hereditary hemorrhagic telangiectasia

Answer: D Type 1 Gaucher disease should be considered in an otherwise healthy young adult with thrombocytopenia and painless splenomegaly. The carrier frequency of mutations in the gene encoding glucocerebrosidase (*GBA1*), which underlies Gaucher disease, is about 1 in 16 in Ashkenazi Jews, in contrast to the carrier frequency in the general population of about 1 in 100. Hurler's disease is a mucopolysaccharidosis that manifests with hepatosplenomegaly, typically in childhood, although patients may live to adulthood. Cystinosis manifests in adults with corneal crystals. Hereditary hemorrhagic telangiectasia is an autosomal dominant disease that is manifested with abnormal blood vessel formations (telangiectasias) of the skin, mucous membranes, lungs, and gut. Fucosidosis manifests in childhood with developmental delay and a neurodegenerative course.

5. The following is true about the association between Gaucher disease and parkinsonism:

- A. All patients with Gaucher disease ultimately develop parkinsonism.
- B. The increased risk of Parkinson's disease is observed only in Ashkenazi Jews.
- C. Mutations in *GBA*, the gene encoding glucocerebrosidase, are extremely rare in subjects with parkinsonism.
- D. An increased frequency of parkinsonism is seen in both patients with Gaucher disease and Gaucher disease carriers.
- E. Lewy body disorders other than Parkinson's disease are not associated with mutations in *GBA1*.

Answer: D Mutations in the glucocerebrosidase gene are one of the most common genetic risk factors for the development of parkinsonism. Both patients with Gaucher disease and Gaucher disease carriers have an increased risk of both Parkinson's disease and related synucleinopathies, such as dementia with Lewy bodies. The increased frequency of *GBA1* mutations is observed in both Jewish and non-Jewish patients with parkinsonism. However, the majority of patients with Gaucher disease never develop Parkinson's disease.

1. A 56-year-old man presents with ectopia lentis and venous thrombosis. What would be the first step in ruling out homocystinuria due to cystathionine β -synthase deficiency?

- A. Rule out Marfan syndrome
- B. Measure cystathionine β -synthase in cultured fibroblasts
- C. Measure total homocysteine and methionine in plasma
- D. Try oral vitamin B6
- E. Sequence the cystathionine β -synthase gene

Answer: C Given the clinical picture, if plasma methionine and total homocysteine levels are elevated, the diagnosis of cystathionine β -synthase deficiency is certain and therapy is urgently needed.

2. A patient is diagnosed with cystathionine β -synthase deficiency. The mutation is not known. What is the best way to start therapy?

- A. Oral aspirin
- B. Oral vitamin B6 along with oral folinic acid
- C. Vitamin B12 injections
- D. Oral vitamin B6 alone
- E. Cocktail of all the vitamins B2, B6, B12, and folinic acid

Answer: B Determination of B6 responsiveness is key as vitamin B6 can be the sole and effective lifelong treatment. Folate repletion with folinic acid supplementation is necessary to permit a pyridoxine response.

3. A 27-year-old woman presents with renal failure, malignant hypertension, and microangiopathic hemolysis. She has early-onset nystagmus and had an unexplained stroke a few years earlier. What do you do?

- A. Start immunosuppressive therapy
- B. Start plasmapheresis
- C. Measure plasma total homocysteine, methionine, and methylmalonic acid and start hydroxocobalamin parenteral injection
- D. Give high-dose folinic acid and betaine
- E. Give vitamin B6

Answer: C Atypical hemolytic-uremic syndrome associated with stroke and nystagmus points toward CblC deficiency. Hydroxocobalamin IM is urgent to correct hemolytic-uremic syndrome.

4. If a cystathionine β -synthase-deficient patient does not respond to B vitamin therapy, what other therapeutic option remains?

- A. Enzyme replacement
- B. Adding cysteine as *N*-acetylcysteine
- C. Dietary methionine restriction
- D. Aspirin administration
- E. Stem cell therapy

Answer: C Dietary methionine restriction is the first line of treatment in pyridoxine-unresponsive CBS deficiency.

5. One should determine plasma total homocysteine if a patient presents with

- A. Neural tube defect
- B. Hypotonia
- C. Stroke before the age of 18 years
- D. Brittle hair
- E. Liver dysfunction

Answer: C Stroke or thrombosis, especially in adolescents and younger adults, should prompt measurement of total homocysteine in plasma because treatments aimed at lowering of total homocysteine levels and reducing (if not abolishing) the vascular risk are available.

Ch / 210 **THE PORPHYRIAS**

1. Which is the most common form of acute hepatic porphyria?

- A. Acute intermittent porphyria
- B. ALA dehydratase deficiency
- C. Hereditary coproporphyria
- D. Porphyria cutanea tarda
- E. Variegate porphyria

Answer: A All forms of acute porphyria are hepatic porphyrias, and acute intermittent porphyria is the most common everywhere except in the South African white population, in which variegate porphyria is locally prevalent as a result of a founder effect. Hereditary coproporphyria is considerably less common than both these forms of porphyria, and ALA dehydratase porphyria is excessively rare, having been described in fewer than 10 patients. Although porphyria cutanea tarda is a hepatic porphyria, it is not an acute porphyria because it presents clinically with skin disease alone and never with acute attacks.

2. The enzyme 5-aminolevulinate synthase 1 (ALAS1) is regulated by

- A. Cytochrome P-450 concentration
- B. Erythrocyte hemoglobin concentration
- C. Free heme pool within the hepatocyte
- D. Iron availability
- E. Substrate availability

Answer: C ALAS1 is the hepatic isoenzyme. When the regulatory free heme pool in the hepatocyte is reduced, ALAS1 is induced, heme biosynthesis is upregulated, and heme levels rise. Conversely, when it is replete, heme synthesis stops. The erythroid isoenzyme ALAS2, by contrast, is principally regulated by iron availability. The availability of the substrates glycine and succinyl coenzyme A is not a limiting factor in heme synthesis. Hemoglobin concentrations are of no relevance to the regulation of hepatic heme synthesis.

3. What is the characteristic clinical presentation of erythropoietic protoporphyria?

- A. Erosions and blisters
- B. Hyperpigmentation
- C. Hypertrichosis
- D. Immediate photosensitivity
- E. Photomutilation

Answer: D Patients with erythropoietic protoporphyria and X-linked protoporphyria complain of immediate photosensitivity, which is manifested as burning, itching, and pain in the skin after a short period of exposure to sunlight. This may be accompanied by erythema and edema. The other options on this list are not characteristic of this form of photosensitivity. Blisters and erosions are typical of the vesiculo-erosive form of cutaneous porphyria noted in variegate porphyria, porphyria cutanea tarda, hereditary coproporphyria, and congenital erythropoietic porphyria. Hypertrichosis may be noted in chronic cases, particularly in porphyria cutanea tarda, and photomutilation is encountered only in the most severe forms of vesiculo-erosive porphyria, such as congenital erythropoietic

porphyria, hepatoerythropoietic porphyria, and the homozygous forms of variegate porphyria and hereditary coproporphyria.

4. Which of the following statements best characterizes the solubility and route of excretion of protoporphyrin?

- A. It is of intermediate water solubility and may be identified in both urine and stool.
- B. It is water insoluble and may be identified in urine.
- C. It is water insoluble and may be identified in stool.
- D. It is water soluble and may be identified in stool.
- E. It is water soluble and may be identified in urine.

Answer: C The different porphyrins vary in their water solubility. The earlier porphyrins, such as uroporphyrin and the porphyrin precursors, are water soluble or hydrophilic and are readily detectable in urine, whereas very little emerges in the stool. Water solubility decreases with each step in the heme biosynthetic pathway. Protoporphyrin is hydrophobic and for practical purposes is undetectable in urine. It is excreted in bile and is therefore identified in stool. Some of the intermediate porphyrins, including coproporphyrin, are of intermediate solubility and detectable in both urine and stool. These properties are important because it is necessary to analyze both urine and stool (as well as plasma and, in the case of erythropoietic porphyrias, in erythrocytes) for an accurate diagnosis.

5. Which of the following treatment modalities is of most importance in modifying the course of the acute attack of porphyria?

- A. Assisted ventilation
- B. β -Blockade
- C. Heme arginate
- D. Liver transplantation
- E. Meperidine

Answer: C Heme arginate is safe and highly effective in terminating the acute attack. When administered early, it will prevent serious complications such as quadriparesis and will reduce the hospital stay. Analgesia is an essential part of management but does not affect the natural history of the attack. β -Blockade may counteract the autonomic activity but is usually not necessary and will not alter the natural course. Assisted ventilation is relevant only in the patient who has had a serious attack with motor neuropathy, quadriparesis, and respiratory failure. Orthotopic liver transplantation is reserved for patients with a severe progressive course marked by recurrent acute attacks.

1. The diagnosis of Wilson disease can be excluded in a patient
- A. If the individual is younger than 21 years
 - B. If a Kayser-Fleischer ring is detected on slit-lamp examination
 - C. If the individual's penmanship is neat
 - D. If results of repeated 24-hour urine copper collections are normal
 - E. If serum ceruloplasmin and serum copper levels are normal

Answer: D Wilson disease may be manifested at any age, although appearance of symptoms before the age of 5 years is rare. The Kayser-Fleischer ring representing copper accumulation in the periphery of the cornea is a diagnostic hallmark of Wilson disease. Dysgraphia is sometimes reported by affected patients, but if it is not present, it should not exclude the diagnosis. The 24-hour urine copper excretion is reliably elevated in Wilson disease, and normal results exclude the diagnosis.

2. All except which of the following are true concerning the diagnosis of Wilson disease?
- A. Schizophrenia in a 20-year-old can be a presenting manifestation.
 - B. Hepatic manifestations usually precede neurologic symptoms.
 - C. Serum copper and serum ceruloplasmin levels are invariably low.
 - D. *ATP7B* mutation analysis is useful for detection of presymptomatic affected individuals.
 - E. Neurologic symptoms often occur later than hepatic signs.

Answer: C An estimated 10% of individuals with Wilson disease have normal serum copper and ceruloplasmin levels, for reasons that remain unclear.

3. *ATP7B* is a copper-transporting molecule that
- A. Mediates copper transport to the brain
 - B. Enables biliary excretion of copper
 - C. Is mutated in Menkes disease
 - D. Has its gene located on the X chromosome
 - E. Is responsible for intestinal copper absorption

Answer: B The Wilson disease gene product, *ATP7B*, normally mediates excretion of copper from the liver into the bile. The gene is located on chromosome 13. *ATP7A* is the gene mutated in X-linked recessive Menkes disease.

4. Low serum copper and ceruloplasmin levels may be found in all except which of the following?
- A. *ATP7A*-related distal motor neuropathy
 - B. Wilson disease
 - C. Aceruloplasminemia
 - D. Menkes disease
 - E. Post-bariatric surgery

Answer: A Serum copper and ceruloplasmin levels are normal in patients with *ATP7A*-related isolated distal motor neuropathy. These can be low in all the other conditions listed.

5. Neurologic presentations of Wilson disease
- A. Never coincide with hepatic symptoms
 - B. Do not include dysarthria, dystonia, rigidity, tremor, or choreiform movements
 - C. Usually involve stroke events affecting the basal ganglia
 - D. Never feature a sensory neuropathy
 - E. Are nearly always (95% of the time) associated with presence of Kayser-Fleischer rings

Answer: E Kayser-Fleischer rings are typically associated with neurologic presentation of Wilson disease. Basal ganglia copper deposition is a pathologic feature in Wilson disease; however, stroke is not.

Ch / 212 **IRON OVERLOAD (HEMOCHROMATOSIS)**

1. How common is the C282Y/C282Y genotype in the United States?

- A. 1 in 70
- B. 1 in 250
- C. 1 in 500
- D. 1 in 1000

Answer: B Numerous large-scale prospective population surveys from North America, Australia, and Europe have determined that the prevalence of the C282Y/C282Y genotype is about 1 in 250 individuals (see Table 212-6).

2. Of individuals who are C282Y homozygotes, what percentage go on to develop phenotypic expression?

- A. 100%
- B. 75%
- C. 50%
- D. 25%

Answer: C Before the discovery of *HFE* in 1996, it was thought by experts in hereditary hemochromatosis (HH) that all patients with genotypic susceptibility would have phenotypic expression. After the discovery of *HFE*, several large population surveys from North America, Europe, and Australia have shown that about half of C282Y homozygotes do not have phenotypic expression. There is highly variable penetrance of C282Y homozygosity (see Definition and Epidemiology).

3. In patients with hemochromatosis who have symptoms, what is the most common presenting complaint?

- A. Arthralgias
- B. Heart failure
- C. Impotence
- D. Complications of cirrhosis

Answer: A Surveys of HH patients who present with symptoms show that arthralgias, usually in the hands and fingers, are the most common. Impotence, heart failure, and cirrhosis with complication are much less commonly seen.

4. Compared with the general population, what is the likelihood for development of hepatocellular cancer in cirrhotic patients with hemochromatosis?

- A. 10-fold increase
- B. 50-fold increase
- C. 200-fold increase
- D. 500-fold increase

Answer: C Cirrhosis from HH results in a major increase in risk for hepatocellular cancer above that in the general population. At one time, there was a concern that extrahepatic malignant disease was also increased, but this has not been confirmed.

5. What is the level of hepcidin in inherited syndromes of iron overload?

- A. Increased
- B. Same as normal
- C. Decreased

Answer: C Inherited syndromes of iron overload should be remembered as hepcidin deficiency conditions. The mechanisms whereby hepcidin regulation results in reduced levels are still to be determined.

1. Which of the following, when included in the diet, is most likely to increase a person's risk for cardiovascular disease?

- A. Monounsaturated fatty acids
- B. *Trans*-fatty acids
- C. Soy protein
- D. Alcohol

Answer: B As noted in the Coronary Heart Disease section of the chapter, hydrogenation of vegetable oils to create margarine and shortening results in the formation of *trans*-fatty acids, which affect serum cholesterol levels in a manner similar to—and are perhaps even worse than—the saturated fatty acids found in butter and lard. The other three choices are all noted in the same section to have potentially protective effects against coronary heart disease.

2. The risk for hypertension is reduced by relatively high intakes of which of the following dietary sources?

- A. Alcohol
- B. Fat
- C. Fruits and vegetables
- D. Sodium

Answer: C As noted in the Hypertension section of the chapter, the Dietary Approaches to Stop Hypertension (DASH) diet, which is rich in fruits, vegetables, and low-fat dairy products and advocates a reduced saturated and total fat content, can decrease blood pressure levels; reducing one's sodium intake provides an additional benefit both alone and when included as part of the DASH diet.

3. Which of the following lifestyle habits is most likely to reduce the risk for chronic diseases?

- A. Multivitamin supplementation
- B. Vitamin A supplementation
- C. Dietary fat restriction
- D. General adherence to dietary recommendations

Answer: D There is no clear evidence that supplementation with multivitamins or vitamin A, or restriction of dietary fat alone, will reduce the risk for chronic diseases. As noted in the Osteoporosis section of the chapter, excessive supplementation with vitamin A reduces bone mass and increases fracture risk. Evidence supports general adherence to dietary recommendations as the best nutritional means to reduce the risk for chronic diseases.

4. Long-term control of the blood glucose level in an obese type 2 diabetic patient is likely to be improved most by which of the following?

- A. Moderate caloric restriction
- B. Fat restriction
- C. Protein restriction
- D. Carbohydrate restriction

Answer: A As noted in the Diabetes Mellitus section of the chapter, dietary carbohydrate restriction is no longer the focus of management of type 2 diabetes, and persons with obesity and type 2 diabetes are best served by weight reduction. This is best accomplished by moderate caloric restriction, not by focusing on restriction of carbohydrates, fats, or protein.

5. A 54-year-old white woman has a bone mineral density that indicates osteopenia in both the spine and hip. Which of the following nutrients may enhance the efficacy of calcium in preserving her bone mineral density?

- A. Vitamin A
- B. Vitamin K
- C. Protein
- D. Sodium

Answer: B As noted in the Osteoporosis section of the chapter, vitamin K assists in maintaining optimal bone mass, whereas excess intakes of vitamin A, protein, and sodium promote bone loss.

Ch / 214 **NUTRITIONAL ASSESSMENT**

1. Which of the following statements is correct regarding clinical nutritional assessment?

- A. Normal values of body mass index (BMI) are higher in women than men in the second through fifth decades of life.
- B. BMI values are useful to grade different levels of obesity or overweight, but not as an indicator of malnutrition.
- C. The use of calipers to measure triceps skinfold is the easiest way to estimate body fat.
- D. The level of hypoalbuminemia cannot be used to predict risk for morbidity and mortality in ambulatory patients.
- E. Adequate feeding in the presence of systemic inflammation increases the serum albumin in malnourished patients.

Answer: C Approximately 50% of body fat is subcutaneous, so the use of skinfold calipers to define the triceps skinfold thickness (TSF) is the most practical technique to estimate body fat. (see Upper Arm Anthropometry section). The same standards of BMI (weight in kilograms divided by the height in meters squared) apply to males and females; and there are BMI standards to define malnutrition (see Body Mass Index section). Hypoalbuminemia is a strong predictor of risk for morbidity and mortality in both hospitalized and ambulatory patients (Van Stijn MF, Korkic-Halilovic I, Makker MS, et al. Preoperative nutrition status and postoperative outcome in elderly general surgery patients: a systematic review. *JPEN J Parenter Enteral Nutr.* 2013;37:37-43). Even though adequate feeding of malnourished patients who have coexisting inflammatory states benefits them in wound healing and immune function, it will not increase serum albumin levels under these conditions (see Serum Proteins section).

2. Which of the following clinical measures provides the most accurate indicator of changes in energy balance and lean body mass in seriously ill hospitalized patients?

- A. Day-to-day weight changes
- B. Isotope dilution
- C. Dual x-ray absorptiometry
- D. Total body nitrogen analysis
- E. None of the above

Answer: E The gold standard for assessing lean tissue is in vivo neutron activation analysis for nitrogen, but this is and will remain a research procedure. Day-to-day weight changes in hospitalized patients generally reflect fluid balance rather than energy balance. Total body nitrogen analysis is likewise primarily a research tool. The other tests listed provide flawed estimates in acute illness (see Assessing Lean Body Mass and Total Body Water section).

3. Which of the following is *not* a risk of full feeding or overfeeding (as opposed to hypocaloric feeding) of critically ill patients?

- A. Hyperviscosity
- B. Hyperglycemia
- C. Fluid overload
- D. Nosocomial infections
- E. Worse postoperative outcomes

Answer: A Hyperviscosity is not known to be associated with full feeding or overfeeding. Hyperglycemia and its attendant increase in risk for nosocomial infections are significant risks, as is fluid overload. Overfeeding should be avoided in postoperative patients who require invasive nutritional support, and modest underfeeding for the first several weeks of acute illness may actually improve outcomes in seriously ill patients (see Measures of Energy Expenditure and Caloric Need).

Ch / 215 **PROTEIN-ENERGY MALNUTRITION**

1. Which one of the following is *not* considered a form of protein-energy malnutrition?

- A. Stunting
- B. Beriberi
- C. Marasmus
- E. Kwashiorkor
- E. HIV wasting

Answer: B Beriberi occurs as a result of vitamin B₁ (thiamine) deficiency and may be due to inadequate intake, malabsorption in the gastrointestinal tract, alcoholism, dialysis, genetic disorders, and other causes (Chapter 218). Although beriberi may be present in patients with protein-energy malnutrition, it is a micronutrient deficiency and would be part of a more global malnutrition syndrome in these patients.

2. Which of the following is the most common underlying factor in childhood mortality worldwide?

- A. Malaria
- B. HIV
- C. Intestinal parasites
- D. Malnutrition
- E. Premature birth

Answer: D Malnutrition, in all of its various forms, is an underlying factor in about 45% of all deaths in children younger than 5 years worldwide.² Although malaria, HIV, intestinal parasites, and prematurity remain extremely common and are a cause of significant mortality and morbidity, malnutrition continues to exceed all of these as a contributing factor to childhood mortality. Malaria accounts for approximately 7% of all childhood deaths, HIV 2%, and prematurity 14%, although each of these numbers would be lower if not for the malnutrition suffered by the mothers and children in question. Intestinal parasites rarely lead directly to mortality, but instead contribute greatly to morbidity, including malabsorptive syndromes and iron deficiency anemia.

3. Which of the following interventions is most likely to be effective in reducing the burden of environmental enteric dysfunction (EED)?

- A. Ensuring all children receive their routine immunizations
- B. Antibiotic prophylaxis
- C. Routine probiotic administration
- D. Zinc supplementation
- E. Albendazole for deworming
- F. Improved sanitation

Answer: F EED is most likely a result of repeated pernicious insults to the intestinal tract that are found most often in developing settings, influenced to a large degree by the lack of sanitation present there in impoverished areas (Korpe PS, Petri WA Jr. Environmental enteropathy: critical implications of a poorly understood condition. *Trends Mol Med.* 2012;18:328-336). Immunizations are unlikely to have an effect on EED because most do not target enteric pathogens, and none target intestinal bacterial or parasitic pathogens. Antibiotics and probiotics have not shown benefit in rigorous clinical prospective clinical trials (Trehan I, Shulman RJ, Ou CN, et al. A randomized, double-blind, placebo-controlled trial of rifaximin, a nonabsorbable antibiotic, in the treatment of tropical enteropathy. *Am J Gastroenterol.* 2009;104:2326-2333). Zinc and albendazole have recently shown modest benefits (Ryan KN, Stephenson KB, Trehan I, et al. Oral zinc or albendazole ameliorates environmental enteropathy in Malawian children: a randomized controlled trial. *Clin Gastroenterol Hepatol.* 2014;12:1507-1513), but these are relatively minimal compared with the degree of benefit that would be expected from modern sanitation systems.

4. Nutritional supply and function of which of the following organs are preserved the longest and most in protein-energy malnutrition?

- A. Brain
- B. Heart
- C. Intestine
- D. Liver
- E. Lung
- F. Skin

Answer: A Nutrient supply to the brain is preserved the longest in patients with protein-energy malnutrition, whereas the other organs must adapt to the decreased nutrients available to them. Nevertheless, some degree of cerebral atrophy is seen, with often permanent irreversible cognitive stunting and developmental delay for children who suffer protein-energy malnutrition.

5. Which of the following is the most useful anthropometric measure for diagnosing acute wasting in a 3-year-old child?

- A. Height
- B. Height-for-age Z-score
- C. Mid-upper arm circumference
- D. Weight
- E. Weight-for-age Z-score
- F. Weight-for-height Z-score

Answer: C The two parameters that are used for diagnosing wasting in all patients are mid-upper arm circumference (MUAC) and weight-for-height Z-score (WHZ). Although WHZ has traditionally been the preferred method for diagnosing acute wasting, MUAC has in recent years proved to be a better predictor of future mortality than WHZ and is now the preferred anthropometric criterion for diagnosing acute wasting. If resources are available to assess both criteria in any given health system, then both should be performed, but this may be tedious, time-consuming, and more expensive (Briend A, Maire B, Fontaine O, Garenne M. Mid-upper arm circumference and weight-for-height to identify high-risk malnourished under-five children. *Matern Child Nutr.* 2012;8:130-133). Height-for-age Z-score and weight-for-age Z-score are useful for diagnosing stunting and underweight, respectively, which are both markers of chronic malnutrition. Height and weight alone do not provide any specific information because there is wide genetic variability in each individual's potential height and weight, and because this is also a function of gender and age.

1. When performing nutritional assessment on a patient in the ICU, the least important factor in the critical care setting is which of the following?

- A. Disease severity
- B. Nutritional intake before admission
- C. Weight as a percentage of ideal body weight
- D. Body mass index
- E. Anthropometric measures

Answer: E Nutritional risk is determined by both evidence of malnutrition and disease severity. Evidence of malnutrition is determined by evaluating body mass index, weight as a percentage of ideal body weight, and nutrition intake before admission. These markers of nutritional status and disease severity then can be combined through an assessment tool such as the NRS 2002 or the Nutric Score to determine overall nutrition risk (see E-Table 216-1). Anthropometric measures such as arm muscle circumference and skinfold thickness have little application in the hospitalized setting.

2. In a critically ill patient with acute sepsis, serum albumin levels are low due to which of the following?

- A. Increased intestinal permeability
- B. Increased vascular permeability
- C. Increased hepatic production of albumin
- D. Shift to greater protein synthesis of skeletal muscle
- E. Increased mobilization of albumin from tissue stores

Answer: B Low albumin levels that follow an acute insult, injury, or admission to an intensive care unit occur because of increased vascular permeability, change in prioritization of hepatic protein synthesis (from proteins of homeostasis to acute phase proteins), and use of albumin as a source of cysteine by the body for antioxidant defense. Serum albumin levels thus represent a negative acute phase response and do not really reflect nutritional status.

3. Which of the following regarding use of the gut in nutrition therapy is true?

- A. The gut contains less than 25% of the immune tissue in the body.
- B. Antigen processing at the level of the gut supports immune tissue localized only within the gut wall.
- C. Bacteria that translocate from the gut migrate out to distant organ sites through the systemic circulation and cause direct infection to that organ.
- D. Maintaining gut integrity suppresses a gut-lung axis of inflammation that would otherwise lead to respiratory failure.
- E. Opening of the paracellular channels between the epithelial cells stimulates blood flow to the mucosa.

Answer: D The gut contains 65% of overall immune tissue of the body and is responsible for 80% of immunoglobulin production. Antigen processing occurs at the level of the gut but supports and delivers immune tissue to distant sites of mucosal-associated lymphoid tissue (MALT), such as the lungs, genitourinary system, and lacrimal glands. Although bacteria and their products may translocate across the gut wall, they rarely make it past mesenteric lymph nodes or the liver. On the rare occasion that bacteria do make it to the systemic circulation, the inoculum is low, and clinical sequelae are minimal. Maintaining gut integrity through provision of enteral nutrition suppresses the gut-lung axis of inflammation, preventing inflammatory cytokines from passing from the gut up through lymphatics to the lung and causing subsequent respiratory failure. Opening the pericellular channels between the epithelial cells is what accounts for increased permeability and allows bacteria within the gut to engage the immune system.

4. Which of the following is true regarding gastric residual volumes as a monitor for aspiration?

- A. Gastric residual volumes correlate well with gastric emptying and risk for aspiration pneumonia.
- B. Decreasing gastric residual volume from 400 to 200 mL protects the patient from aspiration.
- C. Gastric residual volumes in the range 200 to 500 mL indicate a major risk factor for aspiration and should prompt a change in strategy to reduce risk.
- D. Eliminating gastric residual volumes as a monitor of enteral nutrition in the intensive care unit is associated with increased risk for aspiration pneumonia.
- E. Raising gastric residual volumes from 200 to 400 mL will result in fewer occasions for cessation of formula infusion, but the incidence of aspiration may be expected to increase dramatically.

Answer: C Gastric residual volumes correlate poorly with gastric emptying and risk for aspiration pneumonia. Changing the cutoff value for residual volume (up or down) does not change the incidence of aspiration or gastroesophageal reflux. Lowering the cutoff value for gastric residual volumes leads simply to cessation of nutrition therapy. Elevated gastric residual volumes in the range of 200 to 500 mL have been identified as a major risk factor for aspiration and should prompt a change in strategy to reduce risk, such as elevating the head of the bed, initiating prokinetic therapy, and placing the patient in the right lateral decubitus position. Surprisingly, eliminating the use of gastric residual volume as a monitor of enteral nutrition in the intensive care unit is associated with increased delivery of enteral nutrition and no additional adverse sequelae.

5. Ileus during enteral nutrition represents which of the following?

- A. Decreased splanchnic blood flow
- B. Occult infection
- C. Reduced intestinal contractility
- D. Loss of GALT tissue
- E. Reduced gastrointestinal absorptive capacity

Answer: C Ileus represents reduced intestinal contractility in response to acute injury, insult, or critical illness. Early provision of enteral nutrition helps preserve contractility and minimize ileus. Although failure to provide enteral nutrition in the critical care setting does result in reduced splanchnic blood flow, loss of GALT tissue, and reduced absorptive capacity with loss of intestinal villi, ileus relates solely to issues of contractility.

Ch / 217 **MALNUTRITION, NUTRITIONAL ASSESSMENT, AND NUTRITIONAL SUPPORT IN ADULT HOSPITALIZED PATIENTS**

1. A 73-year-old woman with type 2 diabetes mellitus is admitted to the medical intensive care unit (ICU) with abdominal pain on eating on occasion and a 10% weight loss from her usual weight during the past 2 months due to decreased food intake. The patient is obese on physical examination, and skeletal muscle mass cannot be assessed. Which of the following is the most appropriate regarding nutritional assessment?
- A. Malnutrition cannot be assessed.
 - B. An involuntary weight loss of less than 15% during 2 months is not yet a signal for malnutrition.
 - C. The patient is likely to be malnourished.
 - D. Begin parenteral nutrition within 7 days.
 - E. Insert a feeding tube for tube feeds within 2 days of admission.

Answer: C An involuntary weight loss of 10% or more is a classic sign of nutritional inadequacy. Muscle mass cannot be assessed in obese patients accurately in most cases. Use of parenteral or enteral tube feeds for nutrition is indicated only after further evaluation of gut function and oral food tolerance. (Ziegler TR. Parenteral nutrition in the critically ill patient. *N Engl J Med*. 2009;361:1088-1097.)

2. A 23-year-old man with Crohn's disease and chronic, intermittent flares with bloody diarrhea is dependent on oral prednisone (10 mg/day) and is seen in the clinic. He exhibits evidence of skeletal muscle wasting on physical examination. Which of the following is likely to be true?
- A. A combination of protein loss through stool and muscle breakdown from corticosteroids has probably contributed to muscle wasting.
 - B. Use of prednisone at doses of 10 mg/day is unlikely to influence catabolism.
 - C. Inflammation contributes to the patient's muscle loss.
 - D. Iron depletion is unlikely.
 - E. Parenteral nutrition should be started immediately.

Answer: A Protein loss in stool and steroid-induced muscle catabolism probably contributed to muscle loss in this patient. Inflammation also contributes to net body protein catabolism. Iron depletion from stool blood loss is likely. No evidence exists for immediate institution of parenteral nutrition in this setting. (Brown RO, Minard G, Ziegler TR. Parenteral nutrition. In: Ross AC, Caballero B, Cousins RJ, et al, eds. *Modern Nutrition in Health and Disease*. 11th ed. Philadelphia: Lippincott Williams & Wilkins; 2012:1136-1161.)

3. A 65-year-old man with a history of chronic obstructive pulmonary disease exhibits clinical evidence of sepsis and respiratory failure in the emergency department and is admitted to the medical ICU. He is placed on ventilator support. Gut dysfunction is present due to apparent ileus and emesis. The patient's body mass index is very low at 17 kg/m². Which of the following is true?
- A. Parenteral nutrition should be held for at least 8 to 10 days.
 - B. Severely malnourished patients, as in this case, have been shown to be harmed by early parenteral nutrition begun after 4 days of ICU admission.
 - C. A large clinical trial suggests that some patients may have worse clinical outcomes with early (within 2 days) use of parenteral nutrition in ICU settings.
 - D. Tube feedings should be started, regardless of gut function.
 - E. Parenteral micronutrients should be initiated.

Answer: C No clinical practice guideline recommends withholding of parenteral nutrition in patients with gut dysfunction for more than 7 days. A large study showed possible harm from early parenteral nutrition in the ICU (but severely malnourished patients were excluded). Another recent trial showed no difference in mortality at 60 days or length of ICU stay or total hospital days when early parenteral nutrition is started in critically ill patients with relative contraindications to early enteral nutrition. Tube feeds should not be started with clinical evidence of gut dysfunction. Micronutrient

requirements and timing for initiation in the ICU are unclear. (Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med*. 2011;365:506-517. Doig GS, Simpson F, Sweetman EA, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. *JAMA*. 2013;309:2130-2138.)

4. A 55-year-old woman with partial small bowel obstruction precluding any food intake for 10 to 12 days presents to the emergency department and is admitted for failure to thrive. Parenteral nutrition is deemed to be needed for nutritional repletion. Which of the following is true?

- A. Parenteral nutrition with a high dextrose content may cause hypophosphatemia due to insulin-induced movement of phosphorus intracellularly.
- B. Enteral feeding should be instituted as it may prevent bacterial translocation from the gut.
- C. Extra vitamin C should be added to parenteral nutrition as an antioxidant.
- D. Parenteral nutrition should improve gut function in this patient.
- E. Parenteral nutrition containing micronutrients can be initiated after 5 days.

Answer: A High dextrose parenteral nutrition can drive phosphorus intracellularly. Enteral feeds are contraindicated clinically, and there are no data that extra vitamin C or parenteral nutrition would be beneficial. Micronutrient needs in hospital patients are unknown, as is the timing of administration. (Brown RO, Minard G, Ziegler TR. Parenteral nutrition. In: Ross AC, Caballero B, Cousins RJ, et al, eds. *Modern Nutrition in Health and Disease*. 11th ed. Philadelphia: Lippincott Williams & Wilkins; 2012:1136-1161.)

5. A 20-year-old woman is admitted to the trauma ICU after a motor vehicle accident with multiple large bone fractures but no sign of gut dysfunction. She is mechanically ventilated to protect her airway and in anticipation of orthopedic surgery within several days. Which of the following is true?

- A. Parenteral nutrition should be instituted.
- B. Energy needs of the patient probably exceed 300% of normal.
- C. An enteral feeding tube should be placed and enteral feeds initiated within the first 1 or 2 days of ICU admission.
- D. Parenteral nutrition should be used to complement enteral feeds in this patient.
- E. Enteral tube feeds containing adequate energy, protein, and micronutrients can be initiated after 6 days of parenteral nutrition.

Answer: A Most trauma patients can tolerate enteral nutrition, and there is no evidence of gut dysfunction in this patient. Energy needs go up with trauma, but not to 300% of normal. A feeding tube should be placed for institution of early enteral nutrition (within 2 days of admission), but use in such a non-malnourished patient early on is unclear. Optimal timing of enteral nutrition in the ICU remains unclear. (Doig GS, Simpson F, Sweetman EA, et al; Early PN Investigators of the ANZICS Clinical Trials Group. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. *JAMA*. 2013;309:2130-2138.)

1. A 21-year-old woman presents with scarred knuckles, faded wrist scarring, electrolyte imbalance, and low weight (body mass index [BMI] = 20). The menstrual cycle is reported as abnormal and infrequent. The patient denies current abnormal or restrictive eating patterns and self-injurious and compensatory behaviors. The patient expresses clear discomfort during collection of weight and avoids eye contact with clinical staff. No binge eating is reported. What is the most likely diagnosis for this individual?
- A. Anorexia nervosa, general diagnosis: patient exhibits low body weight, potential self-harming behaviors, amenorrhea, and clear discomfort with body weight.
 - B. Bulimia nervosa, general diagnosis: low weight, knuckle scarring, and electrolyte imbalance are consistent with bulimia nervosa.
 - C. Anorexia nervosa, purging subtype: low weight, potential self-harming behaviors, and amenorrhea are consistent with anorexia nervosa; knuckle scarring and electrolyte imbalance are consistent with anorexia nervosa purging subtype.
 - D. No current eating disorder diagnosis: patient's BMI is not *significantly* low within the context of age and sex to indicate a clinical diagnosis of anorexia nervosa, and binge eating and compensatory behaviors are not present.
 - E. Bulimia nervosa, restricting subtype: presence of menstrual cycle, discomfort with body weight, knuckle scarring, and electrolyte imbalance are consistent with bulimia nervosa; low body weight is consistent with bulimia nervosa restricting subtype.

Answer: D The patient's body weight is within a normal range, and denial of abnormal or restrictive eating patterns excludes a diagnosis of anorexia nervosa. Although knuckle scarring and electrolyte imbalance are suggestive of self-induced vomiting, a diagnosis of bulimia nervosa cannot be made without clear indication of the regular use of compensatory behaviors. Although amenorrhea is often a symptom, it is currently neither a necessary nor conclusive criterion for the diagnosis of anorexia nervosa. Although the patient cannot be given a conclusive eating diagnosis, further psychological and physical examination is warranted.

2. A 19-year-old female college student presents with current bulimia nervosa. The patient reports feeling very dissatisfied with her body shape and weight and engaging in binge eating while watching reality television. What is the best *initial* course of treatment action for you to suggest to the patient?
- A. Instruct the patient to modify television preferences to reduce episodes of binge eating while opening up a dialogue with friends about healthy eating habits.
 - B. Refer the patient to a therapist for cognitive-behavioral therapy.
 - C. Prescribe topiramate to help the patient reduce episodes of binge eating.
 - D. Instruct the patient to keep a journal documenting emotions surrounding binge episodes for personal reflection.
 - E. Refer the patient to a therapist for dialectical behavioral therapy.

Answer: B Cognitive-behavioral therapy remains the "gold standard" for the treatment of bulimia nervosa. Although other interventions, such as interpersonal psychotherapy and dialectical behavioral therapy, have shown efficacy in treatment of bulimia nervosa, cognitive-behavioral therapy shows the greatest efficacy across studies and subjects. Although discussing or expressing emotions regarding food and body shape and weight can be helpful for individuals with bulimia nervosa, constructive guidance is generally necessary for symptom reduction and cessation. Although topiramate has been shown to help individuals reduce binge eating, it has a number of cognitive side effects that may make its use impractical.

3. Which of the following is *not* a criterion for the diagnosis of binge eating disorder?

- A. BMI $\geq$ 30 (body mass index obesity threshold)
- B. Marked distress surrounding binge episodes
- C. Binge eating
- D. Lack of regular compensatory behaviors
- E. Weekly episodes of binge eating for at least 3 months

Answer: A There is no weight requirement for a diagnosis of binge eating disorder. Although individuals with binge eating disorder are often overweight or obese, BMI is not a required criterion for the diagnosis.

4. Which of the following statements regarding the genetics of disordered eating is true?

- A. Identical twins are 100% concordant for anorexia nervosa.
- B. Several genes have been conclusively linked to increased vulnerability for eating disorders.
- C. Of the neurotransmitters, dopamine and norepinephrine are the most likely candidates for eating disorder maintenance.
- D. Media generally play a bigger role than genetics in the onset of eating disorders.
- E. Children of individuals with binge eating disorder are more likely to experience out of control eating episodes than anorexia nervosa.

Answer: E Studies show that disordered eating behaviors, such as binge or loss of control eating, are often highly heritable. Offspring of mothers with binge eating have a higher genetic propensity to develop binge eating than do children of mothers who do not exhibit the behavior. Although monozygous twins share equal genetic predisposition for the development of disordered eating behaviors, no eating disorder shows 100% concordance between monozygous twins. Furthermore, although several gene loci have been indicated in the development and maintenance of eating disorders, evidence does not conclusively point to specific genes as responsible for disordered eating. Although studies have indicated the role of norepinephrine in the onset and maintenance of eating disorders, dopamine and serotonin are currently generally considered to be the most likely neurotransmitters to influence disordered eating behaviors. Findings regarding the effect of media on increasing risk for disordered eating are mixed; genetics, however, are strongly implicated.

5. Which of the following is *not* a finding regarding the neuropathology of eating disorders?

- A. Individuals with bulimia nervosa and binge eating disorders are hyper-responsive to food images in reward and somatosensory regions.
- B. Individuals with bulimia nervosa exhibit decreased impulsivity and enhanced inhibitory control relative to control subjects.
- C. Individuals with anorexia nervosa exhibit impaired dopaminergic signaling in striatal circuits.
- D. Individuals with anorexia nervosa exhibit differential activation of fear circuits relative to control subjects.
- E. Findings indicate that dysregulation in the limbic system may be influential in the development of eating disorders.

Answer: B Data suggest that individuals with bulimia nervosa exhibit *increased* impulsivity and *decreased* inhibitory control relative to control subjects.

1. A 52-year-old woman with type 2 diabetes, normal renal function, and a body mass index (BMI) of 36 asks for a referral to a surgeon for evaluation of possible bariatric surgery. Her glycemic control is adequate with a hemoglobin A1c value of 7.2% on 500 mg/day of metformin, 30 U/day of intermediate-acting insulin, and 30 mg/day of pioglitazone. She also has well-managed depression treated with fluoxetine. She has seen a dietitian in the past and has been unable to lose weight. Which of the following is the most appropriate recommendation?

- A. Advise the patient to begin a walking program and refer her to a surgeon with experience in laparoscopic banding procedures.
- B. Advise the patient to begin a walking program and refer her to a surgeon with experience in laparoscopic gastric bypass procedures
- C. Advise the patient to begin a walking program and refer her to a commercial weight loss program that has good outcome results based on peer-reviewed, published data and change the fluoxetine to bupropion.
- D. Advise the patient to begin a walking program, gradually increase the metformin to 2500 mg/day, substitute liraglutide for pioglitazone, and request the dietitian to re-evaluate the patient.
- E. Refer the patient to an academic weight management program that includes cognitive-behavioral therapy and dietary and exercise intervention components.

Answer: D Although the patient's BMI and medical condition technically meet the criteria for bariatric surgery, her previous weight loss attempts have not included a comprehensive program, and she is taking three medications that have weight gain as a side effect. Failure to address iatrogenic causes of weight gain will predispose to medical treatment failure. Surgery should be an option for those who fail to respond to optimal medical management. Pioglitazone and insulin promote weight gain to a greater extent than fluoxetine does, and the decision to change from fluoxetine to bupropion is best made by a clinician responsible for managing her depression. Increasing the metformin to maximum doses and substituting liraglutide for pioglitazone may reduce the need for insulin while maintaining glycemic control. Revisiting dietary strategies is likely to be more effective in the absence of medications that promote weight gain.

2. A 33-year-old woman presents for treatment of obesity. She has been overweight since her teens and experienced net weight gain with each of two pregnancies such that her BMI is now 32.5 kg/m². She had normal glucose tolerance during both pregnancies. Her waist circumference is 29 inches, and her blood pressure in the office is 110/70. Which of the following approaches best matches evaluation/treatment risks and costs with the potential health benefits of weight loss interventions?

- A. Recommend over-the-counter orlistat, advise the patient to begin a walking program, and refer her to a dietitian for instruction in a 1200 kcal/day diet.
- B. Measure thyroid-stimulating hormone, fasting triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, aspartate transaminase, alanine transaminase, and alkaline phosphatase and perform an oral glucose tolerance test to look for hormonal causes of obesity and to screen for metabolic complications. Refer the patient to a dietitian for specific dietary advice based on test results.
- C. Advise the patient to begin a walking program, prescribe phentermine/ topiramate in an extended-release capsule, and refer her to a dietitian for a 1200 kcal/day diet.
- D. Advise the patient to begin a walking program and refer her to a commercial weight loss program that has good outcome results based on peer-reviewed publications.

Answer: D This patient is at low risk for metabolic complications of obesity. She has a low waist circumference for a woman in her BMI range and had no pregnancy-associated glucose abnormalities. Weight gain with pregnancy is common, and in the absence of symptoms of hypothyroidism, laboratory screening is unlikely to be revealing. Costly laboratory testing looking for metabolic abnormalities is likewise a low-yield strategy in this patient. Although this patient is technically a candidate for pharmacotherapy, in practice, the out-of-pocket expense is such that the majority of

patients will not continue with treatment because the amount of weight lost is insufficient. In addition, the side effects and risks of some medications make the risk-to-benefit ratio unappealing. Proven commercial weight loss programs can offer support and education not commonly available in a primary care provider's office. However, providers may wish to confirm that local programs maintain the integrity of the program's published results.

3. A 23-year-old man with a BMI of 56 kg/m² presents in the office after a work screening examination revealed a fasting blood glucose concentration of 180 mg/dL. The patient admits to nocturia for the past 6 months. He has been severely obese since early childhood and reports being frequently hungry and eating large amounts of food. All members of his immediate family are obese. On examination, he has acanthosis nigricans, large amounts of subcutaneous fat, no cushingoid striae, and normal chest and pubic hair. Which of the following further evaluations is most helpful in making disease management decisions?
- A. Administer the Berlin Questionnaire, perform overnight oximetry, and measure hemoglobin A1c, lipids, and liver function.
 - B. Measure serum leptin concentration to test for leptin deficiency and refer the patient to a center with a leptin treatment IND if indicated.
 - C. Perform genetic screening for leptin receptor and melanocortin-4 receptor gene mutations.
 - D. Measure serum testosterone, cortisol, thyroid-stimulating hormone, and growth hormone to screen for endocrine causes of obesity

Answer: A The patient has evidence of sexual maturation, which would not be expected with either leptin deficiency or leptin receptor mutations. Furthermore, there are currently no therapies for patients with leptin or melanocortin-4 receptor gene mutations. Endocrine causes of obesity that begin in childhood would prevent normal adult development (Cushing's syndrome, growth hormone deficiency, hypothyroidism), and testosterone may be low because of obesity. If the patient has sleep apnea, treatment with continuous positive airway pressure is urgently needed, and knowing whether the patient has dyslipidemia or fatty liver disease will inform the urgency of medical or surgical treatment of obesity.

4. A 42-year-old premenopausal woman with type 2 diabetes, dyslipidemia, and a BMI of 44 kg/m² failed to lose a clinically meaningful amount of weight during a comprehensive lifestyle program and is now scheduled for gastric bypass surgery in 1 week's time. In the process of evaluating microcytic anemia and elevated alkaline phosphatase, she is found to have severe iron and vitamin D deficiency. Gastrointestinal studies are negative for bleeding or malabsorption. Which of the following approaches best balances the risks and benefits of treatment?
- A. Prescribe the patient oral vitamin D 50,000 U three times weekly and ferrous sulfate 325 mg, one tablet three times daily, in preparation for surgery.
 - B. Prescribe the patient oral vitamin D 2000 U daily and ferrous sulfate 325 mg, one tablet three times daily, in preparation for surgery. Inform the patient that she will likely need parenteral supplements after surgery.
 - C. Prescribe the patient oral vitamin D 50,000 U three times weekly and ferrous sulfate 325 mg, one tablet three times daily, and defer surgery until her blood levels are replete.
 - D. After surgery, prescribe the patient oral vitamin D 50,000 U three times weekly and ferrous sulfate 325 mg, one tablet three times daily, and monitor blood levels.

Answer: C Bariatric surgery is never an emergency, although many patients are impatient to have this procedure. Absorption of iron, vitamin D, and calcium is often reduced after gastric bypass, making correction of preexisting deficiencies even more difficult. It is highly unlikely that it will be possible to correct this patient's iron and vitamin D deficiencies in 1 week. Aggressive replacement therapy and deferment of surgery until her deficiencies have been corrected will make it easier to manage this patient after bariatric surgery and may improve the surgical risks.

5. A 48-year-old woman, height 175 cm, weight 104 kg, requests treatment for obesity. She states that she has not lost weight following a 1200 kcal/ day diet prescribed by a dietitian despite walking 5 miles/day. Her serum thyroid-stimulating hormone level is normal with no thyroid hormone replacement, and her only medication is an angiotensin-converting enzyme inhibitor for hypertension. She requests instruction in a very low calorie (800 kcal/day) diet and a prescription for a medication to help her lose weight. This patient is most likely to benefit from which of the following approaches?
- A. Refer the patient for measurement of a basal metabolic rate to assess whether she is hypometabolic.
 - B. Ask the patient to use a pedometer to ensure that she is walking 5 miles per day.
 - C. Prescribe an 800 kcal/day high-protein diet and monitor electrolytes carefully.
 - D. Request that the patient complete a real-time diet diary for 2 weeks and weigh the patient when she returns.

Answer: D The patient's basal metabolic rate calculated by the Harris- Benedict formula is 1750 kcal/day, which is likely to be within 10% of her actual metabolic rate if it were measured. It is virtually physiologically impossible for her metabolic rate, let alone total daily energy expenditure, to be less than 1200 kcal/day even if she is not walking at all. Even a very sedentary woman at this height, weight, and age would be expected to expend at least 2000 kcal/day. If she is walking 5 miles, her daily energy expenditure will exceed 2500 kcal/day. The patient must not be following a 1200 kcal/day diet. Self-monitoring of food intake is a proven approach to improve awareness of the types and amounts of food consumed. Many patients will lose weight while self-monitoring, and this approach can help identify problem eating habits. On occasion, patients will record perfect eating habits of unbelievably low energy intake and still not lose weight. Under these circumstances, measurement of a basal metabolic rate may help the physician and patient understand that inaccurate perception of food intake is the issue.

1. Hormones are synthesized and secreted by:

- A. Specialized collections of cells that form endocrine glands
- B. Cells dispersed throughout the lining of the small intestine and within the pancreas
- C. Neurons that comprise the posterior pituitary
- D. The kidney, adipose tissue, and some other organs
- E. All of the above

Answer: E Research has shown that not only classical endocrine glands such as the thyroid and adrenal, but also dispersed enteroendocrine cells in the gut lining and islets in the pancreas, neuroendocrine cells in the posterior pituitary, and non-classical hormone-secreting sites such as kidney, heart, and adipose are all sources of hormone secretion.

2. A genetic hormone deficiency disorder may be caused by:

- A. A mutation in the gene encoding the hormone's signal sequence
- B. Exposure of the pregnant mother to an endocrine "disruptor"
- C. A mutation in a gene encoding an enzyme in the TCA cycle
- D. Paternal advanced age at time of conception
- E. All of the above

Answer: A A mutation in the hormone gene altering the signal sequence of a peptide hormone and thereby impairing its ability to be secreted may cause genetic forms of hormone deficiency such as hypoparathyroidism.

3. Negative feedback suppression is:

- A. The basis for the diurnal rhythm in serum cortisol
- B. The mechanism whereby an "output" regulated by a hormone feeds back to regulate the secretion of that hormone
- C. The basis for menopause in women and lower testosterone with age in men
- D. Always involves one hormone regulating the secretion of another hormone
- E. None of the above

Answer: B B is the correct definition of negative feedback suppression. The latter is not the primary cause of either A or C. D is incorrect because outputs other than hormones can exert negative feedback suppression (e.g., Ca^{++} suppressing PTH secretion).

4. Hormone receptors are:

- A. Always located on the cell surface
- B. When activated, may exert their effects via a second messenger cascade
- C. When activated, may exert their effects by directly regulating gene transcription
- D. Irrespective of starting location, always translocate to the nucleus to exert their actions
- E. Both B and C

Answer: E Because there are cell surface receptors that do not translocate to exert their action, and nuclear receptors for steroid hormones, A and D are incorrect. Both B and C are true for cell surface and nuclear receptors, respectively.

5. Genetic hormone resistance disorders:

- A. Are due to gain-of-function mutations in hormone receptors
- B. Are always due to loss-of-function mutations in nuclear receptors
- C. Are due to overactivity of enzymes that degrade hormones
- D. May be caused by loss-of-function mutations in genes encoding cell surface or nuclear receptors or other components of the signal transduction pathway
- E. Are generally associated with autoimmune disease

Answer: D All the cited examples may be causes of inherited hormone resistance diseases, not just B. A, C, and E do not apply.

1. A 25-year-old woman has had amenorrhea and galactorrhea for 2 years and is found to have hyperprolactinemia. Her PRL level is 513 ng/mL (normal 2.5 to 23.6 ng/mL) and magnetic resonance imaging showed a 1.3-cm macroadenoma. The rest of her evaluation is normal, with the exception of a serum calcium of 11.4 mg/dL. She recalls that one of her cousins also has a pituitary tumor. Which of the following genes should be analyzed for a mutation?

- A. *PROP1*
- B. *Pit1*
- C. *Menin*
- D. *Ret* proto-oncogene
- E. *Ras*

Answer: C Menin is encoded by the gene mutated in multiple endocrine neoplasia (*MEN1*), characterized by multiple endocrine tumors of the parathyroid glands, pancreatic islets, and anterior pituitary, especially prolactinomas. For incorrect answers, see introductory section on “Anatomy and Embryology.”

2. Which of the following medications used to treat pituitary tumor syndromes acts by blocking a hormone receptor?

- A. Pasireotide
- B. Cabergoline
- C. Ketoconazole
- D. Mifepristone
- E. Bromocriptine

Answer: D See Figure 224-8 and its legend.

3. A 67-year-old man is found to have enlarging hands and feet and has been referred by his dentist because of prognathism. To determine whether he has acromegaly, which of the following tests should be carried out?

- A. Pituitary magnetic resonance imaging
- B. Overnight 1-mg dexamethasone suppression test
- C. Insulin-induced hypoglycemia stimulation test
- D. Measurement of insulin-like growth factor (IGF)-I
- E. Inferior petrosal sinus sampling with GHRH stimulation

Answer: D See section on “Diagnosis” under “Growth Hormone Excess: Acromegaly and Gigantism.”

4. Magnetic resonance imaging (MRI) on a 73-year-old woman experiencing dizziness reveals an incidental 3-mm lesion in her pituitary that is compatible with a pituitary adenoma. She has otherwise been well. Testing for hormone oversecretion is negative. What should be the next step in management?

- A. Refer her to an experienced neurosurgeon.
- B. Repeat the MRI in 1 year to look for size change.
- C. Refer her to ophthalmology for a visual field examination.
- D. Begin bromocriptine treatment.
- E. Refer her for a preoperative cardiac stress test.

Answer: B See section on “Clinically Nonfunctioning Pituitary Tumors” at the end of the chapter and also e-Figure 224-1.

1. The hormone vasopressin (AVP) that regulates body water balance is synthesized where?

- A. The anterior pituitary gland
- B. The posterior pituitary gland
- C. The supraoptic and paraventricular nuclei of the hypothalamus
- D. The anterior hypothalamus near the osmoreceptor cells
- E. The principal collecting duct cells of the kidney

Answer: C The supraoptic and paraventricular nuclei of the hypothalamus. The hormones of the posterior pituitary, vasopressin and oxytocin, are synthesized in specialized neurons in the hypothalamus, the neurohypophyseal neurons. These neurons, notable for their large size, are termed *magnocellular neurons*. In the hypothalamus, magnocellular neurons are clustered in the paired paraventricular and supraoptic nuclei (see Fig. 232-1). The synthesized vasopressin prohormone is transported down the axons of the magnocellular neurons to the posterior pituitary gland, where vasopressin is released in response to specific stimuli.

2. Vasopressin secretion is stimulated at what levels of plasma osmolality?

- A. Plasma osmolality above the thirst threshold of 295 mOsm/kg H₂O
- B. Increases of plasma osmolality of 4 to 5%
- C. Increases of plasma osmolality of 2 to 3%
- D. Increases of plasma osmolality of 1 to 2%
- E. Decreases in plasma osmolality of 1 to 2%

Answer: D Increases of plasma osmolality of 1 to 2%. Increases in plasma osmolality as small as 1 to 2% stimulate vasopressin release. Basal plasma levels of vasopressin are generally 0.5 to 2 pg/mL, which is sufficient to maintain urine osmolality above plasma osmolality and urine volume in the range of 2 to 3 L/day. When vasopressin levels are suppressed below 0.5 pg/mL, maximal urine osmolality decreases to less than 100 mOsm/kg H₂O, and a free water diuresis (or “aquaresis”) ensues at levels approaching 800 to 1000 mL/hour (18 to 24 L/day). Increases in plasma osmolality cause a linear increase in plasma vasopressin and a corresponding linear increase in urine osmolality. At a plasma osmolality of approximately 295 mOsm/kg H₂O, urine osmolality is maximally concentrated to 1000 to 1200 mOsm/kg H₂O. Thus, the entire physiologic range of urine osmolality is accomplished by relatively small changes in plasma vasopressin of 0 to 5 pg/mL (see Fig. 232-2).

3. Patients with diabetes insipidus and inability to concentrate their urine usually present with what manifestations?

- A. Polyuria, polydipsia, and hyperosmolality
- B. Polyuria, polydipsia, and dehydration
- C. Polyuria, polydipsia, and hypernatremia
- D. Polyuria, polydipsia, and elevated BUN and creatinine
- E. Polyuria, polydipsia, and normal serum sodium, osmolality, BUN, and creatinine

Answer: E Polyuria, polydipsia, and normal serum sodium, osmolality, BUN, and creatinine. Most patients with diabetes insipidus are not hypernatremic, because the polydipsia produced by a normal thirst response is generally sufficient to maintain water homeostasis. Instead, they present with polyuria, polydipsia, and a normal sodium level and osmolality. Because their fluid intake is sufficient to maintain homeostasis, they are not dehydrated and do not have an elevated BUN or creatinine. In these patients, further testing is necessary to increase serum osmolality and then measure the plasma vasopressin level or the urinary response to an administered vasopressin agonist.

4. After a water deprivation test, a patient increases their urine osmolality from 350 to 375 mOsm/kg H₂O following administration of desmopressin (7% increase). What is the most likely diagnosis?

- A. Primary polydipsia
- B. Nephrogenic diabetes insipidus
- C. Partial hypothalamic diabetes insipidus
- D. Gestational diabetes insipidus
- E. Osmoreceptor dysfunction

Answer: A Primary polydipsia. Adults with normal vasopressin secretion can concentrate their urine to greater than 800 mOsm/kg H₂O and have less than a 10% increase in urine osmolality in response to administered desmopressin. Patients with complete central diabetes insipidus have minimal concentration of the urine with dehydration, and a marked increase in urine osmolality (usually > 50%) in response to administered desmopressin. Patients with nephrogenic diabetes insipidus usually have no increase in urine concentration in response to administered desmopressin, although in some cases of acquired nephrogenic diabetes insipidus, some increased urinary concentration (generally < 10%) can occur. In patients with partial central diabetes insipidus and patients with primary polydipsia, the urine is often somewhat concentrated in response to dehydration, but not to the maximum of a normal person. The chronically reduced level of vasopressin downregulates the synthesis of aquaporin-2 water channels, and the large urine volume, regardless of cause, washes out the medullary osmotic gradient that determines the maximal urine concentration. When desmopressin is administered, patients with partial central diabetes insipidus have a further increase (usually > 10% but < 50%) in urine osmolality, whereas most patients with primary polydipsia have no further increase (i.e., <10%). Patients with gestational diabetes insipidus respond well to desmopressin because desmopressin is resistant to destruction by placental cystine aminopeptidase. Osmoreceptor dysfunction also responds well to desmopressin because it is a variant of central diabetes insipidus, with inadequate osmotic stimulation of vasopressin secretion.

5. What is the treatment of choice for patients with central diabetes insipidus?

- A. Vasopressin
- B. Desmopressin
- C. Thiazide diuretics
- D. Water
- E. Insulin

Answer: B Desmopressin. The best therapeutic agent for the treatment of hypothalamic diabetes insipidus is the vasopressin agonist desmopressin. Desmopressin is different from vasopressin in that the amino group of the N-terminal cystine residue has been removed to prolong the duration of action, and d-arginine has been substituted for l-arginine in position 8 to decrease the vasopressor effects. At therapeutic dosages, this agent acts on V₂ or antidiuretic receptors, with minimal activity at V_{1a} or pressor receptors. Because excess diuresis of water is the primary manifestation of diabetes insipidus, water replacement in adequate quantities avoids the metabolic complications of this disease. However, oral or intravenous administration of the volume of fluid required to replace urinary losses in diabetes insipidus is difficult and inconvenient. Thiazide diuretics and amiloride are useful to reduce polyuria in nephrogenic diabetes insipidus by causing sodium depletion and volume contraction, thereby decreasing urine volume by increasing proximal tubular reabsorption of glomerular filtrate, but do not have as great an effect as desmopressin for hypothalamic diabetes insipidus. Insulin is used to treat diabetes mellitus, not diabetes insipidus.

1. A 74-year-old man with a history of hypertension and hypercholesterolemia is hospitalized after presenting with a 3-month history of progressive fatigue and dyspnea on exertion. His weight on admission is 164 lbs, his pulse is 44 bpm, and lab tests show CPK 528 U/L, TSH 65 mU/L, free T4 0.2 ng/dL, and T4 2.3 µg/dL. A pharmacologic nuclear stress test reveals findings consistent with diffuse myocardial ischemia. Subsequent coronary angiography reveals diffuse three-vessel disease that is not amenable to percutaneous stenting. A consulting cardiologist has recommended that he undergo coronary artery bypass surgery. What would you recommend?
 - A. Start levothyroxine at a dose of 125 µg daily.
 - B. Administer a 60-µg intravenous dose of levothyroxine daily.
 - C. Check antithyroid peroxidase and antithyroglobulin antibodies.
 - D. Start levothyroxine at a dose of 12.5 µg daily.

Answer: D Start levothyroxine at a dose of 12.5 µg daily. This patient requires treatment with levothyroxine, but it should be started at the lowest possible dose, with provisions to gradually increase it as tolerated in light of his coronary artery disease. A full replacement dose given orally or an adjusted dose given intravenously could exacerbate cardiac ischemia to the point of causing an infarction. Checking antithyroid peroxidase and antithyroglobulin antibodies would not provide any additional information. In the absence of any known history of thyroid surgery or external radiation treatment to the head and neck, it can be presumed that his severe hypothyroidism is due to autoimmune thyroiditis.

2. A 28-year-old woman with a 6-year history of hypothyroidism has been treated with levothyroxine at a dose of 125 µg daily. Lab tests checked 5 months ago right before she stopped taking cyclic oral contraceptives showed TSH 1.3 mU/L. Three weeks ago she checked a home pregnancy test that was positive. She had lab tests checked by her obstetrician that showed hemoglobin 10.2 g/dL, T4 12.5 µg/dL, and T3 185 ng/dL. She is estimated to be at 8 weeks' gestation and has started taking prenatal vitamins and iron sulfate at a dose of 325 mg twice daily. What should you do?
 - A. Have her continue levothyroxine at a dose of 125 µg daily, with instructions to take it regularly with other medications.
 - B. Increase her dose of levothyroxine to 150 µg daily.
 - C. Decrease her dose of levothyroxine to 112 µg daily.
 - D. Check a thyroid uptake and scan.
 - E. Check a TSH level.

Answer: E Check a TSH level. The only way to determine whether her current dose of levothyroxine is providing an adequate level of replacement is to check a TSH level. Total T4 and T3 levels measured while taking oral contraceptives or during pregnancy may be elevated or high-normal owing to increased production of thyroxine-binding globulin stimulated by increased estrogen levels. As such, they may not correlate with free thyroid hormone levels. Decreasing her dose of levothyroxine would be inappropriate because she may require a moderate to substantial increase in her dose during the course of a pregnancy. Empirically increasing a dose of levothyroxine may cause iatrogenic thyrotoxicosis characterized by symptoms that may be difficult to distinguish from normal physiologic changes of pregnancy. Exposure to radionuclide tracer is contraindicated during pregnancy, and in any event a thyroid uptake and scan would be unnecessary in a patient with known hypothyroidism. Doses of levothyroxine should always be separated from doses of iron sulfate by at least 4 hours to avoid interactions that can block absorption of both agents.

3. A 76-year-old woman presenting with a 1-week history of a cough, fever, and audible stridor is diagnosed with community-acquired pneumonia. A chest x-ray does not show evidence of an infiltrate but does reveal marked rightward tracheal deviation with a visible mediastinal soft tissue mass. A non-contrast chest computed tomography scan reveals multiple bilateral thyroid nodules, with an 8.5-cm left lower-pole nodule extending below the clavicle and sternum, with compression and narrowing of the trachea. Lab tests show TSH less than 0.001 mU/L, free T4 2.8 ng/dL, and T3 245 ng/dL. A thyroid uptake and scan reveals 24-hour uptake of 37%, with tracer accumulation localized to two right-sided thyroid nodules and the substernal left-sided thyroid nodule. What should you do next?
- A. Check pulmonary function tests with flow-volume loops.
 - B. Prescribe a 12-month course of methimazole 10 mg daily.
 - C. Refer the patient to a thyroid surgeon.
 - D. Administer a 30-mCi dose of I-131.
 - E. Start levothyroxine at a dose of 137 µg daily.

Answer: C Refer the patient to a thyroid surgeon. A multinodular goiter that has extended substernally to the point of causing tracheal compression should be resected by an experienced thyroid surgeon, irrespective of its functional status. The presence of audible stridor and evidence of tracheal narrowing on radiographic images obviates the need for pulmonary function testing with flow-volume loops. Treatment with methimazole might help control hyperthyroidism caused by autonomously functioning thyroid nodules but will not be a permanent solution and would not shrink the dominant nodule to any extent. Treatment with I-131 might help shrink the dominant nodule over time but will require 12 to 24 months to be effective. Treatment with levothyroxine to try to suppress further enlargement of thyroid tissue may be marginally effective at best in euthyroid patients and would be completely ineffective—and potentially dangerous—in an elderly woman presenting with hyperthyroidism.

4. A 33-year-old man is noted to have palpable enlargement of the right side of his thyroid on a routine physical exam. A thyroid ultrasound reveals a solitary 3.1-cm right-sided nodule with smooth borders. Lab tests show TSH 0.1 mU/L and T4 11.5 µg/dL. He reports a history of occasional symptomatic palpitations and weight loss of 5 lbs over the course of 3 months despite an increase in his appetite. He is not taking any medications and has not noted any problems with dysphagia or dysphonia. What should you do next?
- A. Perform a fine-needle aspiration biopsy of the right-sided nodule.
 - B. Administer a 15-mCi dose of I-131.
 - C. Refer the patient to a thyroid surgeon.
 - D. Start methimazole at a dose of 5 mg daily.
 - E. Perform a 123-I thyroid scan.

Answer: E Perform a 123-I thyroid scan. When a patient presenting with a thyroid nodule who is not taking levothyroxine is noted to have a suppressed TSH level, a radionuclide thyroid scan should be checked to determine if the nodule is an autonomously functioning toxic adenoma. If a nodule is “hot” on the scan, it does not need to be biopsied. If it is “cold” on the scan, with evidence of increased tracer uptake in surrounding tissue consistent with Graves disease, fine-needle aspiration biopsy should be performed to confirm it is benign. Treatment of a toxic adenoma or Graves disease with methimazole or radioactive iodine may be indicated but should only be considered after it has been determined whether a biopsy is necessary. Referral for thyroid surgery would only be indicated if a biopsy of a cold nodule revealed suspicious or malignant cytopathology, or if there were contraindications to treatment of a toxic adenoma with radioactive iodine or methimazole.

5. A 55-year-old woman is noted to be tachycardic with a resting pulse of 104 during a routine physical exam. Lab tests checked to evaluate this show TSH 0.002 mU/L, with follow-up lab tests showing free T4 2.3 ng/dL and T3 289 ng/dL. She denies any history of anterior neck discomfort, weight loss, palpitations, anxiety, tremor, heat intolerance, or insomnia. Physical examination reveals tachycardia with a regular rhythm, a slightly enlarged thyroid without any discrete nodularity, and no evidence of proptosis or ocular irritation. She does have a history of osteopenia, with a lumbar spine T-score of -2.3 identified on a DEXA scan checked soon after the onset of menopause. What should you do next?
- A. Check antithyroid peroxidase and antithyroglobulin antibodies.
 - B. Check a radionuclide thyroid uptake and scan.
 - C. Start methimazole at a dose of 10 mg daily.
 - D. Refer the patient to a thyroid surgeon.
 - E. Check an ESR.

Answer: B Check a radionuclide thyroid uptake and scan. This patient is presenting with thyrotoxicosis without any referable symptoms or clinical findings suggestive of a specific cause. Checking a thyroid uptake would help distinguish between a high-uptake state caused by hyperthyroidism driven by increased production of thyroid hormone, and a low-uptake state caused by inflammation with leakage of stored thyroid hormone. If a high-uptake state is identified, a scan will help distinguish whether hyperthyroidism is caused by Graves disease, a toxic adenoma, or a toxic multinodular goiter. Elevated antithyroid peroxidase and antithyroglobulin antibodies may identify underlying autoimmune thyroiditis but will not definitively determine the proximate cause of thyrotoxicosis. Treatment with methimazole or referral for thyroid surgery would only be considered after confirmation of a diagnosis. Checking an erythrocyte sedimentation rate (ESR) would not be informative, because subacute thyroiditis would be unlikely in the absence of localized discomfort.

1. A 35-year-old woman has had weight gain, insomnia, decreased short-term memory, and depression for the last year. She states that her symptoms are worsening. Two recent urine free cortisol (UFC) test results are three-fold increased. She takes lisinopril for recent-onset hypertension. What is the next best diagnostic test?
- A. A 1-mg dexamethasone suppression test
 - B. A pituitary magnetic resonance imaging study
 - C. An adrenocorticotrophic hormone (ACTH) measurement
 - D. Another UFC determination
 - E. A dexamethasone–corticotropin-releasing hormone test

Answer: A Recent guidelines and expert opinion suggest that at least two different screening test results should be abnormal to confirm the clinical suspicion of Cushing syndrome (see Fig. 227-4). This patient has had two abnormal UFC results and should undergo another screening test, either measurement of late-night salivary cortisol or a 1-mg or 2-day 2-mg dexamethasone suppression test. Another UFC determination will not obviate the need for a different screening test. The dexamethasone–corticotropin-releasing hormone stimulation test is more cumbersome and expensive than the dexamethasone suppression test and would not be a better choice. Tests that are used for the differential diagnosis, such as ACTH level or magnetic resonance imaging, should not be used to establish the diagnosis of Cushing syndrome.

2. A 32-year-old white woman with known idiopathic primary adrenal insufficiency complains of recent fatigue and a feeling of being unwell. This has been worse lately when she has been more active with gardening and is worse in the afternoon and evening. She denies dizziness, anorexia, increase in pigmentation, or change in weight. On physical examination, she weighs 125 pounds, with a height of 63 inches. Blood pressure is 110/75, and pulse is 86 without orthostasis. She has pigmented palmar creases and some buccal pigmentation, unchanged from the last visit. There are no other skin lesions. She does not appear cushingoid, there is no abdominal tenderness, and the joint examination findings are normal. Her only medications are hydrocortisone, 15 mg in the morning and 5 mg in the afternoon, and fludrocortisone, 50 mg every other day. What is the next best step?

- A. Measure a plasma renin level
- B. Increase the afternoon hydrocortisone dose to 10 mg
- C. Measure the urine free cortisol excretion
- D. Add a late afternoon hydrocortisone dose of 5 mg
- E. Measure plasma ACTH before the morning hydrocortisone dose

Answer: A This woman has somewhat nonspecific symptoms that are exacerbated by gardening (perhaps by heat). She is receiving adequate hydrocortisone replacement but taking a low fludrocortisone dose. Such nonspecific symptoms may occur in the setting of relative mineralocorticoid deficiency, which can be evaluated through renin measurement. If the renin were elevated, an increased fludrocortisone dose might eliminate her vague symptoms of being unwell. The history and the amount of prescribed hydrocortisone do not suggest that she needs additional glucocorticoid. If she is mineralocorticoid deficient, she might feel better with a higher hydrocortisone dose because of its mineralocorticoid activity; however, a slightly supraphysiologic dose would put her at risk for osteopenia and other features of glucocorticoid excess. (See the section on adrenal insufficiency, assessment to ensure proper dosing.) Measurement of ACTH and urine free cortisol usually is not helpful in assessing adequacy of dosage.

3. A 30-year-old woman presents to the emergency department with the acute onset of nausea, vomiting, diarrhea, and dizziness. Her only medication is levothyroxine, 88 mcg daily. On examination, she is hypotensive, tachycardic, and orthostatic. She has dark skin, and no hyperpigmentation is seen on cursory examination. She has abdominal pain and increased bowel sounds. She is extremely weak but able to move all extremities and to respond to questions. The sodium concentration is 129 mEq/L, potassium concentration is 5.3 mEq/L, and blood urea nitrogen level is 40 mg/ dL. Apart from initiating fluid resuscitation and evaluation for sepsis, what treatment and testing should be ordered immediately?

- A. Draw blood for cortisol measurement before giving hydrocortisone 100 mg IV.
- B. Give dexamethasone 8 mg and perform an ACTH stimulation test.
- C. Measure an ACTH level and give hydrocortisone 100 mg IV.
- D. Give dexamethasone 8 mg and defer further testing.
- E. Give hydrocortisone 100 mg IV and obtain an adrenal computed tomography scan to evaluate for hemorrhage.

Answer: A This woman presents with the signs and symptoms of acute primary adrenal insufficiency. The knowledge that she takes thyroid hormone suggests polyglandular failure. However, it is possible that this constellation of features is caused by sepsis, renal failure, or hypothyroidism. Thus, it is prudent to measure cortisol in blood obtained during intravenous line insertion to confirm the diagnosis of adrenal insufficiency. Other biochemical and stimulation testing can be deferred. She has no apparent reason to have adrenal hemorrhage. Dexamethasone 8 mg is more than what is needed for treatment of adrenal insufficiency; hydrocortisone 100 mg is the recommended initial dose. (See the section on adrenal insufficiency, replacement of adrenal tissue, and treatment.)

4. A 50-year-old man is evaluated for hyperaldosteronism because of difficult-to-control hypertension. He is otherwise healthy. Evaluation was done during treatment with agents that do not affect aldosterone or renin levels and include an aldosterone-to-renin ratio of more than 40 and lack of aldosterone suppression to oral salt loading. A computed tomography (CT) scan of the adrenal glands shows a 1-cm mass on the right with a density of 10 HU. What is the next best step?

- A. Adrenal venous sampling
- B. Right laparoscopic adrenalectomy
- C. Treatment with eplerenone
- D. Review of CT scan to exclude hyperplasia of the left adrenal gland
- E. Ultrasound ablation of the adrenal gland

Answer: A Adrenal venous sampling should be performed to identify the source of excess aldosterone.

It is possible that the visualized mass is a nonfunctioning tumor. This man is a good surgical candidate, and laparoscopic adrenalectomy would be recommended if venous sampling is consistent with unilateral disease. The CT scan is not helpful in identifying bilateral disease. Treatment with eplerenone and ultrasound ablation would be possibilities if he were not a surgical candidate; eplerenone would be an appropriate treatment for bilateral disease. (See section on mineralocorticoid excess, diagnosis and treatment.)

5. A 35-year-old woman presents with a 6-month history of increasing body hair growth. Before that time, she states that she was mildly “hairy” but now needs to shave her face daily. (She has stopped shaving for 3 days so that her hair growth would be visible.) She has had only two episodes of vaginal spotting during this time. Her menses started at the age of 13 years and are usually irregular, occurring every 30 to 45 days. The extra hair growth started in her teens and until 6 months ago was similar to the hair pattern of her mother and sister. She admits to some recent irritability and perhaps has gained 5 pounds. She has always had a low voice and does not notice any recent change. She has a 3-year-old daughter. She has been able to continue her 35 minutes of daily cardiovascular exercise. On physical examination, body mass index is 30, blood pressure 125/85 mm Hg, pulse 82. The Ferriman-Galway score is 17. Fat distribution is normal with some increased abdominal fat, and she appears “well developed” but not especially muscular. There is no temporal hair recession, but her scalp hair appears thin. Acne is present on the chest and back. The clitoral index is 100 mm. Laboratory results include low luteinizing hormone and follicle-stimulating hormone, estradiol 50 pg/mL, dehydroepiandrosterone sulfate (DHEA-S) 653 ng/dL (reference range, 4 to 332), and testosterone 235 ng/dL. These abnormalities are confirmed on a second set of tests. What is the next best diagnostic step?

- A. Obtain a CT scan of the adrenal glands
- B. Obtain an ovarian ultrasound
- C. Perform a 1-mg overnight dexamethasone suppression test
- D. Measure a morning 17-hydroxyprogesterone level
- E. Measure an androstenedione level.

Answer: A This woman has recent-onset hirsutism and virilization. Whereas worsening polycystic ovary syndrome is a possibility, the degree of DHEA-S and testosterone elevation suggests the possibility of an adrenal tumor. The slight weight gain and irritability might also point to possible cortisol excess. Although androstenedione would confirm an adrenal source, it is unlikely to point to another cause, and so proceeding to adrenal CT scan is reasonable, particularly because adrenal cancer is part of this differential diagnosis. An ovarian ultrasound is less likely to be abnormal (i.e., an ovarian tumor is less likely). Congenital adrenal hyperplasia is consistent with these signs and symptoms but not with the time course of rapid worsening. Cushing syndrome is a possibility, but it is less likely to be Cushing disease with these levels of hormones; adrenal cancer is a possibility that would be identified by the CT scan, making a 1-mg dexamethasone suppression test less urgent. (See the section on androgen excess.)

1. An effective class of antihypertensive drugs could be based on which of the following?

- A. Postsynaptic α 1-receptor agonists
- B. Presynaptic α 2-receptor agonists
- C. Tyrosine hydroxylase activators
- D. β 1-Receptor agonists
- E. β 2-Receptor agonists

Answer: B See introduction section of the chapter on catecholamines and adrenergic receptors. Agonism at the presynaptic α 2-receptor is the only option listed that would decrease catecholamine synthesis or release. Central α 2-receptor agonists are Food and Drug Administration–approved antihypertensive drugs (e.g., clonidine, guanfacine).

2. Your patient has a disease-causing mutation in succinate dehydrogenase subunit D (*SDHD*) and is currently pregnant. She asks you if her child inherits the *SDHD* mutation from her, what is the chance that her child will develop a paraganglioma in his or her lifetime? You advise her that if her child inherits the *SDHD* mutation, the risk for development of a paraganglioma is closest to

- A. 0%
- B. 25%
- C. 50%
- D. 75%
- E. 100%

Answer: A See section on familial paraganglioma under Pathobiology and Genetics. In patients with *SDHD* mutations, penetrance depends on the mutation's parent of origin. Hence, the disease does not manifest when the mutation is inherited from the mother but is highly penetrant when it is inherited from the father. This phenomenon is known as maternal imprinting.

3. In a patient with an incidentally discovered adrenal mass, which of the following imaging characteristics is consistent with pheochromocytoma?

- A. Lack of enhancement with intravenous contrast medium on computed tomography (CT)
- B. Low signal intensity on T2-weighted magnetic resonance imaging (MRI)
- C. Homogeneous mass with absent cystic and hemorrhagic changes
- D. Precontrast CT Hounsfield unit density (e.g., >20 HU)
- E. Rapid contrast washout with more than 50% washout at 10 minutes

Answer: D See section on diagnosis. Imaging characteristics of an incidentally discovered adrenal mass consistent with pheochromocytoma include increased baseline CT Hounsfield unit density (e.g., >20 HU); marked enhancement with intravenous contrast medium on CT; high signal intensity on T2-weighted MRI; cystic and hemorrhagic changes; bilaterality; and large size (>4 cm). In addition, pheochromocytomas are characterized by slow contrast washout (e.g., <50% at 10 minutes after administration of contrast material).

4. Medications and agents that frequently increase measured levels of catecholamines and metanephrines include

- A. β -Adrenergic inhibitors
- B. Presynaptic α 2-receptor agonists
- C. Tyrosine hydroxylase inhibitors
- D. Tricyclic antidepressants
- E. Calcium-channel blockers

Answer: D See Table 228-2. In addition, β -adrenergic inhibitors do not affect circulating levels of catecholamines or metanephrines in a clinically important way. Central α -receptor agonists (e.g.,

clonidine) decrease the release of catecholamines. Tyrosine hydroxylase is the rate-limiting step in catecholamine synthesis, and inhibition of this step decreases total body catecholamine production. Use of tricyclic antidepressants is the most common cause of false-positive results of biochemical testing for pheochromocytoma.

5. In preparing the patient with pheochromocytoma for surgery, which of the following statements is correct with regard to β -adrenergic blockade?
- A. The β -adrenergic antagonist should be administered before the α -adrenergic blocker is started.
 - B. It is indicated to control the tachycardia associated with both the high concentrations of circulating catecholamines and the α -adrenergic blockade.
 - C. The dosing of the β -adrenergic antagonist is not affected by asthma or congestive heart failure in this unique setting of catecholamine excess.
 - D. The dose of the β -adrenergic antagonist should be titrated for a heart rate of 50 beats per minute.
 - E. The dose of the β -adrenergic antagonist should be titrated for a systolic blood pressure of 100 mm Hg.

Answer: B See medical therapy section on treatment. The β -adrenergic antagonist should be administered only after α -adrenergic blockade is effective; with β -adrenergic blockade alone, hypertension may be more severe from the unopposed α -adrenergic stimulation. Preoperative β -adrenergic blockade is indicated to control the tachycardia associated with both the high concentrations of circulating catecholamines and the α -adrenergic blockade. The clinician should exercise caution if the patient is asthmatic or has congestive heart failure. Chronic catecholamine excess can produce a cardiomyopathy that may become evident with the initiation of β -adrenergic blockade, resulting in acute pulmonary edema. Therefore, the β -adrenergic blocker should be administered cautiously and at a low dose.

1. A 51-year-old man has a history of type 2 diabetes mellitus for 6 years. Past medical history is significant for chronic hepatitis C infection, chronic kidney disease stage 3, and a recent hospitalization for an upper gastrointestinal bleed. He takes a sulfonylurea for blood glucose control and rarely checks his blood glucose level. Fasting plasma glucose concentration in the office is 195 mg/dL, and his HbA1c is 6.8%. What do you conclude about his glucose control?
 - A. His average blood glucose concentration during the past 3 months is approximately 140 mg/dL.
 - B. HbA1c may be falsely high because of chronic kidney disease.
 - C. HbA1c may be falsely low because of liver disease.
 - D. HbA1c levels are increased after acute blood loss.
 - E. HbA1c levels are more reflective of postprandial than of fasting glucose concentration.

Answer: C This patient has several reasons that his HbA1c may not accurately reflect his mean plasma glucose concentration. HbA1c results may be influenced by a number of factors, including conditions that alter red cell survival or cause interference with a specific assay. The HbA1c may be falsely low in this patient because of cirrhosis (increased red cell turnover), recovery from recent acute blood loss (greater percentage of younger erythrocytes with shorter exposure to glucose), or transfusion (dilution of patient's blood with nondiabetic donor blood). In these instances, measurement of glycated serum proteins (fructosamine) or direct measurement of plasma glucose concentration will more accurately reflect glycemic control.

Additional information about HbA1c assay methodology and interpretation of results can be obtained from the National Glycohemoglobin Standardization Program: <http://www.ngsp.org>.

2. A 38-year-old woman has had type 1 diabetes mellitus since the age of 12 years. She has maintained excellent control (HbA1c 6.0%) with a basal/ bolus injection regimen. She tests her glucose level four or five times a day, and review of her meter download shows many glucose levels in the 30s and 40s. However, the patient is unconcerned because she has no symptoms at these times. On questioning, she admits to recently "spacing out" while driving, which led to a minor traffic accident. Regarding the etiology and treatment of hypoglycemia in this patient:
 - A. She has adapted to low blood glucose concentration and no change in treatment is required.
 - B. She has developed hypoglycemia unawareness and her target HbA1c should be increased.
 - C. Strict avoidance of hypoglycemia is of little benefit in reversing hypoglycemia-associated autonomic failure.
 - D. An excessive counter-regulatory hormone response to hypoglycemia may contribute to her lack of symptoms.
 - E. Treatment with β -blocker should be considered.

Answer: B In patients with long-standing diabetes, the counter-regulatory systems that normally would counteract the decline of glucose to dangerous levels may be impaired. This is especially true for patients with type 1 diabetes, who often have defects in glucagon and epinephrine response during hypoglycemia. This decrease in epinephrine response during hypoglycemia is accompanied by an attenuated autonomic neural response, which results in the clinical syndrome of *impaired awareness of hypoglycemia*. Without autonomic symptoms, mild hypoglycemia may proceed unnoticed to more advanced and dangerous phases. There is, however, evidence that hypoglycemia-associated autonomic failure can be reversed by strict avoidance of hypoglycemia, which can be facilitated by increasing target glucose levels.

Reno CM, Litvin M, Clark AL, Fisher SJ. Defective counterregulation and hypoglycemia unawareness in diabetes: mechanisms and emerging treatments. *Endocrinol Metab Clin North Am*. 2013;42:15-38.

3. A mother brings her 19-year-old son, who has type 1 diabetes and uses an insulin pump, to see you and to ask for referral to a dietitian. She complains that her son refuses to follow his “diabetic diet” and frequently eats junk food, including fast food (burgers, fries, pizza) and ice cream. She also worries that he sometimes skips meals, saying he is not hungry. His body mass index is 22, and his recent laboratory results show an HbA1c of 7.8%, low-density lipoprotein cholesterol of 95, and normal triglycerides. Which of the following dietary recommendations is most appropriate for this patient?

- A. An 1800-calorie/day American Diabetes Association diet
- B. A low-carbohydrate diet
- C. A low-protein diet
- D. A low-fat, high-fiber diet
- E. A flexible “heart healthy” meal plan that limits concentrated sweets and emphasizes fruits and vegetables

Answer: E Dietary recommendations for patients with diabetes have changed substantially over time, from the extremely low-carbohydrate, high-fat diets used before the discovery of insulin as a therapy, to “exchange diets,” to more flexible meal plans. For patients with type 1 diabetes, the key element is for the patient to learn to match mealtime insulin doses to the carbohydrate content of the meal. Severely restricted diets (very low carbohydrate or low calorie) are neither required nor advisable, although avoidance of large carbohydrate loads will help minimize post-meal glycemic excursions. For most patients with type 2 diabetes who are typically overweight or obese, moderate carbohydrate intake and reduction in total calories are advised. Current recommendations allow a variety of eating styles and ethnic food preferences, with emphasis on fruits and vegetables, low-fat protein sources, and use of monounsaturated or polyunsaturated fats.

Evert A, Boucher J, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 2013;36: 3821-3842.

Lasa A, Miranda J, Bullo M, et al. Comparative effect of two Mediterranean diets versus a low-fat diet on glycaemic control in individuals with type 2 diabetes. *Eur J Clin Nutr*. 2014;68:767-772.

4. A 54-year-old woman presents to her physician for treatment of hypertension. She had gestational diabetes during her last pregnancy 15 years ago, and there is a family history of type 2 diabetes (mother and older brother). Her body mass index is 36. Fasting glucose concentration is 110 mg/dL, and HbA1c is 6.2%. Which of the following have been shown to reduce the progression to diabetes in high-risk patients?

- A. Weight loss by reduced calorie diet
- B. Treatment with metformin
- C. Treatment with acarbose
- D. Bariatric surgery
- E. All of the above

Answer: E This patient has multiple risk factors for the development of type 2 diabetes, including family history, prior history of gestational diabetes, obesity, and hypertension. In addition, her glucose and HbA1c levels are already elevated above normal, in the defined “pre-diabetes” range. All of the treatments listed have been shown to prevent or to delay the onset of diabetes in randomized clinical trials. The most consistent evidence comes from weight loss trials. Both the Finnish Diabetes Prevention Study and the U.S. Diabetes Prevention Program reported 58% reduction in diabetes with a hypocalorie, reduced fat diet combined with moderate-intensity physical activity. Weight loss achieved with bariatric surgery is also highly effective in preventing (or even reversing) diabetes. Medications, including metformin, the α -glucosidase inhibitor acarbose, and troglitazone (a thiazolidinedione), have also been shown to reduce diabetes in high-risk patients, although somewhat less effectively than by lifestyle modification. Lifestyle changes and metformin are reported to be cost-effective interventions, but whether delay or prevention of type 2 diabetes will result in lower rates of cardiovascular disease and diabetes microvascular complications will require longer-term follow-up studies.

Schwarz PE, Greaves CJ, Lindstrom J, et al. Nonpharmacologic interventions for the prevention of type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2012;8:363-373.

5. A 28-year-old woman with type 1 diabetes since the age of 12 years is considering having a child. Currently, her blood glucose is reasonably well controlled, although she admits this was not the case during her teens and early 20s, when her HbA1c was in the 9 to 11% range. She has mild background diabetic retinopathy, normal blood pressure, urine albumin-to-creatinine ratio of 25 mg/g, and normal findings on foot examination. Which of the following is true?

- A. She should delay pregnancy until she has achieved optimal glucose control (HbA1c ~6.5%).
- B. She should be treated with an angiotensin-converting enzyme inhibitor to prevent progression of renal disease during pregnancy.
- C. Progression of her retinopathy during pregnancy is likely to result in vision loss.
- D. The risk of her child's developing type 1 diabetes is 25 to 50%.
- E. She should be advised to avoid pregnancy because of the risk of both maternal and fetal complications.

Answer: A Although pregnancies in women with type 1 diabetes are generally considered “high risk,” the outlook for patients with minimal complications and good metabolic control is good. Women with advanced renal disease (proteinuria, reduced glomerular filtration rate) or proliferative retinopathy may experience rapid progression during pregnancy because of the influence of hormonal and hemodynamic changes and should be monitored closely by specialists. Use of angiotensin-converting enzyme inhibitors is contraindicated during pregnancy because of the risk of fetal renal damage. The key to successful pregnancy outcomes is achieving optimal glucose control before conception because the developing fetus is most susceptible to the teratogenic effects of hyperglycemia in the first 6 to 8 weeks of pregnancy, before the time that most women are aware of being pregnant. Maintaining strict glucose control during the pregnancy will reduce the risk of fetal complications, such as macrosomia and hyperbilirubinemia. Many patients benefit from use of an insulin pump and continuous glucose monitoring during this time. Although a child of a mother with type 1 diabetes is at increased risk of diabetes compared with the general population, the risk is less than 10%.

1. Which of the following is true in relation to glucose physiology?

- A. Insulin stimulates gluconeogenesis.
- B. Glycogenolysis predominantly takes place in the kidney.
- C. Lipolysis is dependent on ketogenesis.
- D. Glucagon stimulates glycogenolysis.
- E. Pancreatic beta cells stop producing insulin when the blood glucose level reaches 2.4 mmol/L.

Answer: D Glucagon stimulates glycogenolysis and releases stored glucose.

2. In the counter-regulatory hormonal response to hypoglycemia:

- A. Growth hormone is the first hormone to increase in response to a falling blood glucose level.
- B. Serum cortisol levels increase in parallel to glucagon.
- C. Adrenaline and noradrenaline are the first line of defense against a falling blood glucose level.
- D. Pancreatic delta cells produce glucagon in response to hypoglycemia.
- E. The main glucosensors for hypoglycemia are located in the carotid body.

Answer: C Adrenaline and noradrenaline are the first line of defense against a falling blood glucose level. Adrenaline and noradrenaline with glucagon are the key counter-regulatory hormones produced in response to a falling blood glucose level.

3. Which of the following does *not* constitute Whipple triad?

- A. A low measured plasma glucose concentration
 - B. Symptoms and/or signs compatible with hypoglycemia
 - C. Occurrence of any symptoms and/or signs during hypoglycemia
 - D. Resolution of symptoms and signs when glucose concentrations are corrected
- Answer: C** Whipple triad includes a low measured plasma glucose concentration, symptoms and/or signs compatible with hypoglycemia, and resolution of symptoms and signs when glucose concentrations are corrected.

1. Which of the following polyglandular neoplastic syndromes is **not** caused by a germline mutation?

- A. McCune-Albright syndrome
- B. MEN 1
- C. Carney complex
- D. von Hippel-Lindau disease
- E. MEN 2

Answer: A The polyglandular neoplastic syndromes are all due to germline mutations in either tumor suppressor genes (*MEN1*, *MEN4*, Carney complex, *VHL*) or in an oncogene (*MEN2*). Only McCune-Albright syndrome is due to a somatic mutation, but because the mutation may occur early in embryogenesis, multiple endocrine and nonendocrine organs may be affected.

2. A 25-year-old man presents with kidney stones and is found to be hypercalcemic with an elevated PTH. All the following steps are indicated **except**:

- A. Ultrasound localization of parathyroids and immediate parathyroidectomy
- B. Take a careful family history and consider screening first-degree relatives for hypercalcemia.
- C. Consider testing the patient for anterior pituitary and pancreatic islet lesions.
- D. Test the patient's germline DNA for *MEN1* gene mutations.

Answer: A Age 25 is quite young to present with primary hyperparathyroidism on a sporadic basis and raises suspicion of familial disease, particularly MEN 1. Steps in B through D are indicated because a positive family history for parathyroid, anterior pituitary, and/or pancreatic islet tumors would bolster the likelihood of MEN 1, as would positive results of screening for pituitary and pancreatic islet disease, and of course if *MEN1* gene mutation is identified.

3. A 35-year-old woman with type 1 diabetes and Hashimoto's thyroiditis presents for routine follow-up. She has no specific complaints, and her physical examination is normal except for a small thyroid gland. Which additional screening test should be done to evaluate adrenal function?

- A. Measurement of antiadrenal antibodies
- B. Measurement of morning serum cortisol
- C. No screening test is necessary; adrenal insufficiency is unlikely
- D. A Cortrosyn stimulation test

Answer: A Antiadrenal antibodies predict the development of adrenal insufficiency, and in the absence of clinical features are a reasonable screening test in this woman with a high probability of having autoimmune polyglandular syndrome 2. One might argue that no test is needed in the absence of clinical symptoms; however, many would advocate measurement of the antibodies, which if positive, might increase the frequency of clinical surveillance.

4. A patient with autoimmune adrenal insufficiency and type 1 diabetes presents with complaints of abdominal discomfort and occasional diarrhea. This is not precipitated by food. She does not have orthostasis, nausea, vomiting, or joint aches and otherwise feels well, although she recently lost 5 pounds. What is the next best step?

- A. Consider increasing her hydrocortisone dose to test whether this represents subtle glucocorticoid deficiency.
- B. Measure tissue transglutaminase (TTG) antibody to exclude celiac disease.
- C. Assess gastric motility to evaluate for gastroparesis.
- D. Measure liver function tests to exclude hepatitis.

Answer: B This patient may have celiac disease, which is associated with autoimmune adrenal insufficiency. These symptoms do not suggest that the other conditions are more likely.

5. A 22-year-old woman with autoimmune polyglandular syndrome (APS) 1 mentions during a routine visit that she is thinking of becoming pregnant. She wants to know whether she will pass on the disorder to her child and what genetic testing should be done. She is not related to her partner. You reassure her that it is extremely unlikely that her child will have APS 1 because of its recessive genetic transmission. What else should you tell her regarding testing for the *AIRE* gene.

- A. She could get the *AIRE* gene tested to see if her child will carry a mutation.
- B. Her partner could get the *AIRE* gene tested to see if her child will carry a mutation.
- C. The child should be tested for *AIRE* mutations at birth.
- D. No gene testing is necessary.

Answer: D Her child will be an obligate carrier of an *AIRE* haplotype mutation; this is not sufficient to cause the disease and does not need to be documented by analysis of her mutations. Given that she is not related to her partner, it is unlikely that he will carry a mutation, thus testing of the partner is not indicated. There is no reason to test the child at birth.

Ch / 232 **NEUROENDOCRINE TUMORS AND THE CARCINOID SYNDROME**

1. A 56-year-old woman presents with diarrhea, episodes of facial flushing, and fatigue. An enlarged liver is noted on exam, and a computed tomography scan shows metastatic nodules within the liver. A biopsy of one of these nodules shows a well-differentiated neuroendocrine tumor. The most likely primary site for this cancer is:

- A. Thymus
- B. Lung
- C. Stomach
- D. Small intestine
- E. Rectum

Answer: D Small bowel carcinoid with hepatic metastases is the neuroendocrine tumor most commonly associated with carcinoid syndrome (General Reference 5).

2. Evaluation to identify a primary tumor site and corroborate the diagnosis in the patient in question 1 should include:

- A. FDG-PET scan
- B. Echocardiogram
- C. Upper endoscopy
- D. Bone scan
- E. Radionuclide-labeled somatostatin receptor ligand imaging

Answer: E Most (80%) low-grade neuroendocrine tumors will have somatostatin receptors (Grade A Reference A2).

3. Initial therapy for the patient in question 1 should be:

- A. Octreotide
- B. Chemoembolization of hepatic metastasis
- C. Everolimus
- D. Surgical tumor debulking
- E. Benadryl

Answer: A Octreotide reduces symptoms of flushing and diarrhea in the majority of patients and should be used before any surgical intervention to prevent carcinoid crisis (General Reference 6).

4. A 24-hour urine for 5-HIAA is collected from the patient in question 1 and found to be elevated at 180 mg excretion per 24 hours (normal, <10 mg/day). The increased secretion of serotonin is associated with all of the following **except**:

- A. Flushing episodes
- B. Diarrhea
- C. Hepatic metastasis
- D. Risk of carcinoid heart disease
- E. Development of pellagra

Answer: A Histamine and catecholamines (the latter as the trigger) but not serotonin are the mediators of carcinoid flushing in many cases. Serotonin is most likely responsible for diarrhea, valvular heart disease, and niacin deficiency. In patients with carcinoid syndrome, up to 60% of dietary tryptophan may be used to form 5-HTP and 5-HT. Because tryptophan is used to form nicotinic acid, depletion of the latter in such patients can result in symptomatic pellagra.

5. The prognosis for the patient listed above is most likely:

- A. Cure following surgical resection
- B. 4- to 6-month survival
- C. 1- to 2-year survival
- D. 4- to 6-year survival
- E. >10-year survival

Answer: D Metastatic neuroendocrine tumors are rarely curable, but because of their slow rate of growth, appropriately managed patients may live many years with good quality of life (General References 1 and 10).

1. Bilateral inguinal masses are palpated on routine examination of a newborn girl. There is a patent vaginal orifice. A karyotype is 46,XY. Which of the following disorders is *not* a possibility in this child?

- A. Complete androgen insensitivity
- B. 17-Hydroxylase deficiency
- C. 11 β -Hydroxylase deficiency
- D. 5 α -Reductase deficiency
- E. 17-Ketosteroid reductase deficiency

Answer: C This is a genetic male who has testes, with female-appearing external genitalia. The failure of development of normal male external genitalia must be due to failure of biosynthesis (answers B, D, or E) or action (answer A) of the most potent androgen, dihydrotestosterone. Deficiency of 17-hydroxylase (B) prevents synthesis of all androgens; 5 α -reductase deficiency (D) prevents conversion of testosterone to dihydrotestosterone, and 17-ketosteroid reductase deficiency (E) prevents conversion of androstenedione to testosterone. In contrast, 11 β -hydroxylase deficiency (answer C) is associated with increased secretion of androgen precursors by the fetal adrenal gland, which causes virilization of affected 46,XX female fetuses but no genital abnormality in males.

2. An 8-year-old boy has bilateral inguinal hernias and bilateral cryptorchidism. The penis and scrotum are normal. At operation, a uterus and fallopian tube are noted in the left inguinal canal, following which the surgeon terminates the operation and pages you, the on-call endocrinologist. What gene is *most likely* affected in this patient?

- A. AMHR2 (anti-müllerian hormone receptor)
- B. CYP21A2 (steroid 21-hydroxylase)
- C. SRY (sex-determining region Y)
- D. SF1 (steroidogenic factor 1)
- E. LHGCR (luteinizing hormone receptor)

Answer: A This boy has persistent müllerian duct syndrome, which can be caused by mutations in either anti-müllerian hormone or (equally likely) in its receptor. Persistence of müllerian structures (uterus and fallopian tubes) in this otherwise normal boy prevents descent of the testes. CYP21A2 mutations (answer B) do not cause any abnormalities of reproductive structures in 46,XY males. Affected 46,XX females might have virilization of the external genitalia that could be severe enough to be mistaken for males and would indeed have a normal uterus and fallopian tubes. However, such individuals almost invariably develop adrenal insufficiency shortly after birth, and all newborns in the United States are screened for this disorder. Moreover, the müllerian structures in females with CYP21A2 mutations are found in their normal positions because there are no testes and spermatid ducts to drag them into the inguinal canals. Mutations of SRY (answer C), SF1 (D), and LHGCR (E) are found in 46,XY phenotypic females.

3. A 15-year-old girl presents for evaluation of primary amenorrhea. She has Tanner 5 breasts and an adult female distribution of pubic and axillary hair. There are no inguinal or labial masses. An ultrasound examination shows ovaries in the normal position but no uterus. The patient's karyotype and diagnosis are *most likely* to be which of the following?

- A. 46,XY; complete androgen insensitivity syndrome
- B. 45,X/46,XX mosaic; Turner syndrome
- C. 46,XY; 17,20-lyase deficiency
- D. 46,XX; Mayer-Rokitansky-Küster-Hauser syndrome
- E. 46,XX; Kallman's syndrome

Answer: D Patients with Mayer-Rokitansky-Küster-Hauser syndrome have normal ovaries and therefore have normal female secondary sexual characteristics. By definition, they have atresia of the uterus and upper vagina. This phenotypic female has axillary and pubic hair, meaning that she responds normally to androgens secreted by the adrenal glands and (if present) by the ovaries. This rules out complete androgen insensitivity syndrome (answer A); 46,XY males with that condition have absent or sparse axillary and pubic hair. Moreover, they have testes that are often palpable in the inguinal canals or labia. Girls with Turner syndrome (answer B) often have pubic and axillary hair (owing to adrenal androgen secretion) and may have some degree of breast development, owing to local aromatization of adrenal androgens in breast fat and (if mosaic) to some residual ovarian function. But the uterus is normally formed. 46,XY males with 17,20 lyase deficiency (answer C) cannot synthesize androgens and have a phenotype similar to patients with complete androgen insensitivity syndrome. Patients with Kallman's syndrome (answer E) have hypogonadotropic hypogonadism; affected females indeed have primary amenorrhea and may or may not have development of secondary sexual characteristics depending on degree of severity, but they have normal development of the uterus.

4. A 13-year-old boy is brought to your office by his parents because he insists that he is really a girl. He has had this feeling as long as he can remember, but it is causing him increasing distress now that he is in early adolescence. He has insisted on wearing dresses or gender-neutral clothing whenever possible. On examination, he is at the 50th percentile for height and weight for boys for his age. He has downy hair on his upper lip, axillary hair, a normally formed penis with the urethral meatus at the tip of the glans, bilaterally descended 4-mL testes, Tanner stage 2 pubic hair, and 1 cm of firm glandular tissue under each nipple. What would be the single most informative evaluation at this point?
- A. Psychology consultation
 - B. Karyotype
 - C. Serum levels of dehydroepiandrosterone, androstenedione, and testosterone
 - D. FSH and LH
 - E. Estradiol

Answer: A Any patient with gender dysphoria requires psychological evaluation, preferably in the context of evaluation by an experienced multidisciplinary team, before considering any medical management. Transgendered patients rarely have identifiable medical etiologies for their condition unless the history and physical examination raise suspicion for a DSD. This phenotypic boy has palpable testes, strongly suggesting that he is 46,XY (answer B), and a normally formed penis, strongly suggesting intact ability to synthesize androgens (answer C). He has age-appropriate development of secondary sexual characteristics, suggesting that his ability to secrete gonadotropins is intact (answer D). Mild gynecomastia is typical in boys in early to mid-adolescence (owing to aromatization of androgens in breast tissue, in the context of low testosterone levels relative to adults) and is without clinical significance; estradiol levels will not be elevated.

5. You are paged to the intensive care nursery to evaluate a 2300-g term infant for ambiguous genitalia. The baby developed respiratory distress at delivery and is now intubated on a respirator. You are told that a cleft palate was noted on intubation. You hear a grade 3/6 harsh holosystolic murmur. The baby has accessory digits bilaterally. The penis is small and the urethral meatus is at the base of the shaft. There is a bifid scrotum; gonads are palpable bilaterally in the inguinal canals. What laboratory tests are *most likely* to establish the diagnosis?
- A. 17-Hydroxyprogesterone and androstenedione
 - B. Testosterone and dihydrotestosterone
 - C. Androstenedione and testosterone
 - D. 11-Deoxycortisol and cortisol
 - E. 7-Dehydrocholesterol and cholesterol

Answer: E This male infant has Smith-Lemli-Opitz syndrome, owing to an inability to synthesize cholesterol from its immediate precursor. He is small for gestational age and, as a term infant, must have serious cardiorespiratory dysfunction (such as lung hypoplasia) to require ventilator support. The character of the murmur suggests a ventriculoseptal defect. The other physical findings are all typical of this syndrome. Boys with 5 α -reductase deficiency are unable to synthesize dihydrotestosterone from testosterone (answer B); they may have female-appearing or ambiguous genitalia, but have no other medical problems. Boys with 17-ketosteroid reductase deficiency cannot synthesize testosterone from androstenedione (answer C); the phenotype is identical to 5 α -reductase deficiency. Patients with 11-hydroxylase deficiency cannot synthesize cortisol from 11-deoxycortisol (answer D). Males are phenotypically normal; females may have ambiguous genitalia but no other congenital anomalies.

1. A 22-year-old man presents to his primary care physician with decreased libido and loss of morning erections. He had a recent low-impact fracture of his right tibia. His height was 185 cm and weight was 230 pounds. Laboratory tests included a serum testosterone of 96 ng/dL on a sample obtained at 4:00 pm and serum LH of 1.0 mIU/mL. Which of the following information is *not* necessary in the evaluation of this patient?

- A. DEXA scan of the hip and spine
- B. Karyotype to evaluate for Klinefelter' syndrome
- C. Serum prolactin level
- D. Repeat serum testosterone obtained between 7:00 am and 10:00 am
- E. MRI of the sella with and without gadolinium

Answer: B This patient has a low serum testosterone consistent with his clinical complaints. A DEXA scan is appropriate because he had a low-impact trauma and low serum T is a risk factor for osteoporosis and fractures. The serum testosterone should be repeated even though it is very low because it was collected in the afternoon and serum testosterone declines because of diurnal variation. An MRI and prolactin are appropriate because the low serum testosterone is coupled with a low serum LH, thus raising the possibility that the patient has hypogonadotropic hypogonadism, which could be due to a pituitary mass lesion that might be secreting prolactin (prolactinoma).

2. A 37-year-old man presented to his primary care physician complaining of inability of he and his wife to conceive. They have been married for 3 years. She is 27 years old, is not on contraceptives, and has regular menstrual periods. Neither has had a prior pregnancy. His semen specimen showed no spermatozoa in the ejaculate with a specimen volume of 3 mL. The man has a serum testosterone of 240 ng/dL and serum LH and FSH levels were 2 to 3 times above the upper reference range. A karyotype was XXY. The most appropriate recommendation would be:

- A. Referral to a urologist for consideration of testicular sperm extraction and intracytoplasmic sperm injection into eggs obtained from his wife.
- B. MRI of the sella.
- C. Treatment with HCG and FSH.
- D. Treatment with clomiphene.
- E. Repeat karyotype.

Answer: A This patient has Klinefelter's syndrome as diagnosed by karyotype. Other than artificial insemination of the partner using donor spermatozoa partner or adoption of a child, the best approach to achieve fertility would be to attempt to extract spermatozoa by testicular sperm extraction and intracytoplasmic sperm injection into oocytes obtained from his female partner. The success rates depend on whether the urologist can find spermatozoa in the testis and the quality of the spermatozoa and the oocyte. There is no need for an MRI of the sella or treatment with HCG or clomiphene, because LH and FSH levels are elevated and a pituitary/hypothalamic lesion is not likely. A repeat karyotype could be done but is not necessary because everything fits the present diagnosis of Klinefelter's syndrome.

3. A 75-year-old man complains of erectile dysfunction (ED). His libido is mildly decreased. He has had two previous myocardial infarctions and is being treated with a calcium channel blocker for hypertension. His morning serum testosterone is 380 ng/dL, with serum LH and FSH in the normal range. The best first-line treatment is:

- A. Transdermal testosterone to increase his serum testosterone to over 500 ng/dL.
- B. An aromatase inhibitor.
- C. A β -blocker to reduce the stress levels of the penis.
- D. Phosphodiesterase-5 (PDE-5) inhibitor.
- E. Referral to a psychologist to evaluate for psychogenic erectile dysfunction.

Answer: D This elderly man has ED without hypogonadism. The first-line treatment is a PDE-5 inhibitor to increase the vasodilatory functioning in the penis. The other treatments are unnecessary because they are directed toward treatment of primary or secondary hypogonadism (use of testosterone or aromatase inhibitors). A β -blocker is not an effective treatment for ED.

4. An 82-year-old man has decreased libido, decreased muscle strength, and osteopenia on DEXA scan. He has a strong family history of prostate cancer. A serum testosterone level was 300 ng/dL with a free testosterone by equilibrium dialysis that is below the reference range. Serum LH was in the high-normal range. A PSA was 7 ng/mL. The best strategy is to:

- A. Treat with a 5 α -reductase inhibitor.
- B. Treat with testosterone to reverse the manifestation of hypogonadism.
- C. Refer to a urologist for assessment of his prostate.
- D. Treat with an aromatase inhibitor to reduce estradiol levels.
- E. Ignore his complaints because it is normal and acceptable for age

Answer: C The appropriate first-line approach is to refer to a urologist to rule out prostate cancer. The patient is elderly and hypogonadism might be present, but his total testosterone is 300 ng/dL with a low free testosterone that is probably the result of an age-associated increase in SHBG. Even if he were hypogonadal, his PSA is elevated, thus requiring a prostate assessment. Although the clinical symptoms are important to the patient, all treatments (testosterone replacement, use of an aromatase inhibitor to increase endogenous testosterone levels) must be delayed until the prostate risk is assessed. Treatment with a 5 α -reductase inhibitor is not appropriate until he has been assessed for possible prostate cancer.

5. A 50-year-old obese man complains of low libido. He had a serum testosterone checked by liquid chromatography tandem mass spectrometry; it was 190 ng/dL. A serum LH level was above the reference range for adult men. The physician decided to treat the patient for hypogonadism with testosterone replacement. Which one of the following adverse events is the most commonly seen?

- A. Elevated LDL cholesterol
- B. Anemia
- C. Hypercalcemia
- D. Priapism
- E. Erythrocytosis

Answer: E Testosterone increases red blood cell mass by several mechanisms. An increase in both hemoglobin and hematocrit of 5 to 7% from baseline after testosterone is not uncommon. The increase in hemoglobin and hematocrit is dose dependent. Elevation of hematocrit to greater than 54% or hemoglobin greater than 17 g/dL requires either phlebotomy or the withdrawal of testosterone until the hematocrit and hemoglobin decrease into the reference range. Anemia may be seen in testosterone deficiency but not with testosterone treatment. With physiologic replacement of testosterone, LDL cholesterol levels are not elevated. Hypercalcemia does not occur as a result of testosterone therapy. Priapism may occur with PDE-5 inhibitors but not with testosterone treatment.

1. The testis-determining factor sex-determining region Y (SRY) directly induces differentiation of which one of the following?

- A. Sertoli cells
- B. Leydig cells
- C. Spermatocytes
- D. Spermatids
- E. Spermatozoa

Answer: A SRY expression leads to the differentiation of Sertoli cells and expression of müllerian-inhibiting substance (or antimüllerian hormone) by these cells. It does not play a role in the differentiation of Leydig cells (which is induced by thyroid hormone and luteinizing hormone, or the various developmental groups of spermatozoa development (which develop in the presence of testosterone). (See Embryogenesis and Differentiation.)

2. In utero, oocyte meiosis arrests at which stage?

- A. Prophase
- B. Metaphase
- C. Anaphase
- D. Telophase
- E. Interphase

Answer: A During oogenesis, oocytes enter the first phase of meiosis but halt at the diplotene stage of prophase 1. The process of maintaining the prolonged resting state of meiosis is called dictyotene and continues until puberty. Progression beyond the prophase (metaphase, anaphase, telophase, or interphase) involves chromatin condensation and could limit the molecular function of the oocyte DNA. (See Embryogenesis and Differentiation.)

3. Which one of the following is true of precocious puberty in girls?

- A. Is diagnosed when pubertal changes occur before 10 years of age
- B. Can occur earlier in white girls compared with African American girls
- C. Can result in masculine pubertal development
- D. Requires premature activation of the hypothalamic-pituitary axis
- E. Is less likely to be pathologic if diagnosed at an earlier age

Answer: C Precocious puberty is diagnosed if puberty commences before 9 years of age in white girls and 8 years of age in African American girls. It can result in either isosexual or heterosexual pubertal development. If the cause is central, then the hypothalamic-pituitary-ovarian (HPO) axis is activated; however, noncentral causes (e.g., exogenous gonadal hormone exposure) do not require activation of the HPO axis. The earlier the age of the girl, the more likely it is to be pathologic. (See Precocious Puberty.)

4. Delayed menarche is caused by dysfunction in which one of the following?

- A. Hypothalamus
- B. Pituitary
- C. Ovary
- D. Uterus
- E. All of the above

Answer: E Delayed menarche can result from the absence of gonadotropin-releasing hormone pulsatility, disruptions in gonadotropin release from the pituitary, loss of functional oocytes, or obstruction of the outflow tract, to name a few. Disruptions at any point along the female reproductive axis can result in disruptions in the orderly transition through puberty. (See Delayed Puberty.)

5. The diagnosis of polycystic ovarian syndrome (PCOS) absolutely requires which one of the following?

- A. Evidence of oligo-ovulation or anovulation
- B. Evidence of hyperandrogenism
- C. Evidence of polycystic-appearing ovaries by imaging
- D. Exclusion of other disorders that can cause menstrual irregularity and hyperandrogenism
- E. All of the above

Answer: D The diagnosis of PCOS requires two of the following three: evidence of oligo-ovulation/anovulation, hyperandrogenism, and/or polycystic-appearing ovaries. No one of them is absolutely required. However, ruling out other disorders that can appear to be PCOS must be done before PCOS can be diagnosed. (See Polycystic Ovarian Syndrome.)

Ch / 236 **REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY**

1. Which of the following is the main biologic mediator that causes menstrual cramping?

- A. Follicle-stimulating hormone (FSH)
- B. Prostaglandin
- C. Estradiol
- D. Inhibin
- E. Aromatase

Answer: B Prostaglandins increase in concentration during the luteal phase, and their release results in greater and/or prolonged uterine contraction. This excessive contraction results in ischemic pain. Prostaglandin synthesis inhibitors decrease prostaglandin concentration and thereby alleviate dysmenorrhea. FSH stimulates granulosa cell production of estradiol and is predominant before ovulation. Estradiol is a gonadal hormone involved in the development of female secondary sexual characteristics and reproduction but does not induce menstruation or menstrual pain. Inhibin is released from the follicle to downregulate FSH production by the pituitary. Aromatase converts testosterone to estradiol. (See Cyclic Changes in Target Organs: Endometrium; and Harel Z. Dysmenorrhea in adolescents and young adults: an update on pharmacological treatments and management strategies. *Expert Opin Pharmacother.* 2012;13:2157-2170.)

2. Which of the following directly regulates the secretion of gonadotropin-releasing hormone (GnRH)?

- A. Endogenous opiates
- B. Follicle-stimulating hormone (FSH)
- C. Luteinizing hormone (LH)
- D. Follistatin
- E. Antimüllerian hormone

Answer: A GnRH secretion is regulated by neurotransmitters and neuromodulators, including endogenous opiates (see Neuroendocrine Regulation of the Ovaries). FSH and LH release are regulated by GnRH, but there is no direct feedback mechanism with these molecules. Instead, FSH and LH act on the ovary to produce gonadal hormones, which can impact GnRH release. Follistatin binds to activin and regulates activin's activity on gonadotropin production but does not itself directly regulate GnRH. Antimüllerian hormone is produced by the follicle and can be used as a marker for ovarian reserve but does not regulate GnRH secretion.

3. Endometriosis is most likely to cause which of the following?

- A. Menorrhagia
- B. Premenstrual syndrome
- C. Dyspareunia
- D. Ovarian hyperstimulation
- E. Amenorrhea

Answer: C Rationale: Endometriosis is defined as the presence of endometrial glands and stroma outside of the uterine cavity, and typical clinical characteristics are infertility and dysmenorrhea. Endometriosis-related peritoneal scarring can also result in dyspareunia and dyschezia. (See Abnormalities of the Reproductive Years: Dysmenorrhea and Endometriosis: Definition.) Endometriosis does not significantly influence menstrual flow and therefore does not cause menorrhagia or amenorrhea. Premenstrual syndrome occurs before menstruation and has not been demonstrated to be caused by endometrium outside of the uterine cavity. Ovarian hyperstimulation occurs typically with exogenous gonadotropin use, resulting in massive enlargement of the ovaries and ascites. It is not caused by endometriosis.

4. Among women with hypergonadotropic amenorrhea (premature ovarian failure or insufficiency), what is the lifetime likelihood of delivering a live-born progeny using their own oocytes?

- A. Same as in normal population
- B. 1 in 2
- C. 1 in 5
- D. 1 in 15
- E. Less than 1 in 10,000

Answer: D The lifetime likelihood of delivering a live-born child using their own (e.g., autologous) oocytes is 6 to 8% in this patient population. (See Hypergonadotropic Amenorrhea: Treatment.) As a result, women with this condition should not be managed expectantly, regardless of age. Standard therapies directed at inducing ovulation (clomiphene citrate, letrozole, or gonadotropins) are also not indicated because these women are already exposed to high gonadotropins and are unlikely to respond to exogenous sources. Should such patients desire pregnancy, the most effective intervention requires the use of donor oocytes.

5. Which of the following is the infertility treatment most likely to cause triplet pregnancy?

- A. Clomiphene citrate
- B. Letrozole
- C. Bromocriptine
- D. Controlled ovarian stimulation with intrauterine insemination
- E. Controlled ovarian stimulation with in vitro fertilization

Answer: D Clomiphene citrate induces ovulation by inhibiting estradiol-mediated feedback, thereby increasing endogenous gonadotropins. Although twinning is common (8%), triplets or more are rare. Letrozole is an aromatase inhibitor that decreases estradiol production and thereby decreases estradiol-mediated negative feedback on gonadotropins in a manner similar to clomiphene. Again, there is minimal evidence of high-order multiple pregnancies. Bromocriptine is used in hyperprolactinemic women to induce normal ovulation, and multiple pregnancies are rare. When exogenous gonadotropins are used without oocyte retrieval, there is a risk for fertilization of multiple mature oocytes, resulting in a twin rate of 30% and a higher order multiple rate of 5%. (See Infertility: Treatment.) When oocytes are retrieved, and the number of embryos transferred to the uterus is limited, the risk for higher order multiples drops to 1%.

1. Which of the following is the reason to consider teratogenicity of medication in 30-year-old women who are not currently pregnant?
- A. Half of all pregnancies in the United States are unplanned, putting the fetus at risk.
 - B. Many medications have long half-lives and can affect the fetus even if stopped at the time of conception.
 - C. Almost all medications are known to be unsafe in the first trimester.
 - D. Women in their 30s are less likely than younger women to identify that they are pregnant in the first weeks of pregnancy.

Answer: A Half of all pregnancies in the United States are unplanned, including those in women in their 30s and 40s. Most women will not begin prenatal care until 12 weeks' gestation, after which major organogenesis has occurred. It is therefore incumbent on the prescribing physician to consider the impact of the medications they prescribe in any patient of childbearing potential.

2. The decision to undergo screening mammography in women aged 40 to 49 years should be shared decision making because of all except which of the following?
- A. Breast cancer is less common than lung cancer in this age group.
 - B. Overdiagnosis of breast cancer may result in detecting cancers that would not require treatment.
 - C. Women in their 40s have a higher false-positive rate of screening studies than women older than 50 years.
 - D. Women tend to overestimate their breast cancer risk and benefit from education and discussion of risks and benefits.

Answer: A U.S. Preventive Services Task Force guidelines recommend shared decision making for women of average risk aged 40 to 49 years for screening mammography, given the potential harms of both a higher false-positive rate and overdiagnosis. Several studies indicate that normal-risk women in this age group tend to overestimate their personal breast cancer risk.

3. Management of a non-ST elevation acute coronary syndrome (ACS) in women should differ from men in which of the following ways?
- A. Medical management is preferred over revascularization in women but not in men.
 - B. Noninvasive testing is not recommended in women.
 - C. Aspirin is not indicated for emergent treatment of ACS because of bleeding risk.
 - D. β -Blockers should be avoided because of increased risk for congestive heart failure.
 - E. Lipid management goals are low-density lipoprotein cholesterol levels of less than 120 mg/dL.

Answer: A Medical management of ACS and non-ST elevation myocardial infarction is the same for men and women, with aspirin, β -blocker, thrombolytic therapy, noninvasive testing, and cardiovascular rehabilitation. Randomized trials suggest that medical management has better outcomes than early revascularization in women with non-ST elevation myocardial infarction (MI) only, but not in men, one place where gender differences in guidelines exist. Early revascularization is recommended for women and men with ST elevation MI.

4. A woman taking fluoxetine for depression is now planning pregnancy. In counseling her, you would advise which of the following?
- A. If possible, she should switch to sertraline.
 - B. She should wait until the pregnancy test is positive, then stop the medication.
 - C. An increase in dose should be considered if depressive symptoms increase in pregnancy.
 - D. To avoid fetal abnormalities, she should stop the medication before attempting conception.

Answer: C Although several studies have suggested a possible association between selective serotonin reuptake inhibitor (SSRI) use in pregnancy and fetal anomalies, these associations usually disappear in

studies that are able to control for other causes of fetal abnormalities such as smoking, and in those that are able to ascertain that the SSRI is the only prescription used. Fluoxetine appears to have fewer concerns than sertraline in the available studies. Because of drug distribution in pregnancy, increased doses in pregnancy may be required. The benefits of treated depression and the risks for depression to the woman and her child, including evidence of some developmental delays, must be weighed against any small increased risk for fetal anomalies.

5. Screening for problem alcohol use in women should consider all except which of the following?

- A. Binge alcohol drinking is common in women.
- B. Younger women have an alcohol threshold (amount and duration) for complications that is lower than men.
- C. Women develop complications from alcohol abuse with lower intake for shorter time periods.
- D. Rates of alcohol dependence in women are about 5%.

Answer: B Although women have lower rates of alcohol dependence (5%) compared with men (10%), they develop complications with lower amounts of alcohol and with short length of abuse. Binge drinking is common not only among young adults but also among those older than 30 years, and it puts women at risk for violence and poor choices, including sexually transmitted diseases and sexual assault.

Ch / 238 CONTRACEPTION

1. A 34-year-old nulliparous woman requesting contraception is found to have a blood pressure of 165/90 mm Hg. Otherwise, her screening for medical contraindications is negative. Which contraceptive methods would *not* be appropriate for her?

- A. Progestin-only pills (POPs)
- B. Combined oral contraceptives (COCs)
- C. Copper-containing IUD
- D. Etonogestrel subdermal implant
- E. Levonorgestrel-IUS

Answer: B According to the Medical Eligibility Criteria, this level of hypertension is considered a category 4 contraindication for COCs. Hypertension is considered category 2 for POPs and implants, and it is category 1 for the copper IUD. Nulliparity is considered a category 2 condition for the copper IUD.

2. What would you advise a woman who comes seeking protection from one act of unprotected intercourse 60 hours before her visit?

- A. Have a copper IUD inserted.
- B. Find a regular method of contraception.
- C. Fill a prescription for ulipristal emergency contraception (EC).
- D. Buy a package of levonorgestrel emergency contraception if other alternatives are not readily available to her.
- E. All of the above

Answer: E The clinician should give the woman the choice of how to proceed after explaining the options and their advantages and disadvantages. The IUD works as emergency contraception in this time frame, but there is no large series of data on use of the progestin-containing device as opposed to the copper IUD, largely because it was not available when the earlier studies were done. The time period after exposure is associated with a diminution of efficacy for LNG EC pills, but there is probably still some effect, and they are easy to obtain. Ulipristal works in this time frame, but it must be

supplied by prescription and is costly in the United States unless it is covered by insurance. Women who find themselves in need of EC should review their usual contraceptive practices and try to find an effective method that suits them for regular use.

3. A woman calls your office saying that she took her last combined oral contraceptive (COC) pill 3 days ago. She was traveling and lost her pill pack, and she has now returned home. She had sex yesterday and the day before, both times using a male condom, but she thinks the condom broke yesterday. What would you advise her?

- A. Start taking a new pack of COC pills immediately.
- B. Take two pills today and tomorrow.
- C. Use condoms for the next 7 days.
- D. Take levonorgestrel emergency contraception.
- E. A, C, and D

Answer: E For any scenario with missed pills, women should take a pill as soon as it noticed to be late, and then continue taking one at the usual time. At the most, this would require taking two pills once; repeated days of double-dosing of pills is not recommended. Condoms must be used until the woman is back on COCs for 7 days. Because there is the possibility that the condom broke and she had unprotected sex within the last 24 hours, she should consider taking emergency contraception.

4. What contraceptive method would you recommend for a woman seeking protection from sexually transmitted infection (STI) and pregnancy who wishes to use only one method?

- A. Combined oral contraceptives
- B. Progestin-containing IUD
- C. Female condom
- D. Male condom
- E. Spermicides

Answer: D Hormonal contraception does not protect against the acquisition of infection. Spermicides, although toxic to infectious organisms in vitro, do not seem to provide protection against STIs in vivo, and the irritation of the genital tract caused by these compounds may create a portal of entry for pathogens. The female condom is also not a proven method to protect against HIV and other sexually transmitted pathogens, but there is a suggestion that it may reduce risk. The only well-studied method that clearly prevents both pregnancy and STI transmission is the male condom.

5. A woman had a copper IUD inserted 3 weeks ago and complains that she cannot feel the strings in her vagina. On speculum examination, the strings are not visible. On pelvic ultrasound, a bright echogenic linear structure is noted within the uterine cavity. Her vital signs and examination are otherwise normal. What is the appropriate diagnosis and next step?

- A. The IUD is correctly placed, but the strings have withdrawn into the uterine cavity. Reassure her that the IUD will be effective; no further action is necessary.
- B. The IUD has perforated the uterus. The patient must be scheduled for laparoscopic removal of the misplaced IUD.
- C. The IUD is misplaced. It must be removed and replaced in order to be effective.

Answer: A The ultrasound confirms that the IUD is correctly placed within the uterus. Even though the strings are not visible, the IUD will be effective. At the time of removal, small forceps may be used to grasp the strings, which are likely in the endocervical canal or lower portion of the uterus. There is no evidence of perforation in this case.

1. A 30-year-old G1P0 at 36 weeks' gestation presents with a complaint of right upper quadrant pain. She denies nausea, vomiting, change in color of urine or stool, or change in the pain with eating. She does state that she has had a dull headache and "floaters" in her vision. Laboratory testing reveals an aspartate aminotransferase level of 82 (upper reference limit = 40), hemoglobin level of 14.3, creatinine concentration of 1.0, and platelet count of 100,000. What is her most likely diagnosis?

- A. Cholelithiasis
- B. Acute hepatitis
- C. Cholestasis of pregnancy
- D. Preeclampsia
- E. Migraine syndrome

Answer: D This patient is a primigravida who presents in her third trimester with symptoms of preeclampsia, hemoconcentration, elevated creatinine for pregnancy, and thrombocytopenia, all most suggestive of preeclampsia.

2. You are caring for a 36-year-old patient with a 6-year history of type 2 diabetes. She has been erratically controlled with metformin, 500 mg daily, and basal insulin. She has never been pregnant but is considering starting a family. What is the single most important advice you can give her?

- A. She is really too old to begin a family.
- B. She needs to achieve normoglycemia and normalize her hemoglobin A1c level before conception.
- C. She will need to be tightly controlled during pregnancy, so she needs to call you as soon as she has a positive pregnancy test result.
- D. She needs an eye examination before pregnancy.
- E. She should see a nephrologist to screen her kidney function before pregnancy.

Answer: B This patient is in an ideal circumstance for preconception counseling. Normalization of her glucose concentration and hemoglobin A1c level before conception will lower her risk of fetal congenital anomalies and spontaneous abortion to background risk levels.

3. A 24-year-old G2P1 woman whom you observe for asthma comes in at 14 weeks' gestation. She has had increasing problems with her asthma, needing a rescue inhaler two or three times a day, and has had nocturnal awakening. She denies chest pain, recent upper respiratory infection, gastroesophageal reflux, or new exposures. What is the most likely cause of her asthma exacerbation?

- A. The normal effects of pregnancy
- B. The increased work load and oxygen consumption associated with pregnancy
- C. She has discontinued her steroid inhaler and controller medication because of concern about the drug's effect on the fetus.
- D. She has decreased her exercise.
- E. The stress of work, pregnancy, and sleep deprivation

Answer: C The most frequent cause of asthma exacerbation in pregnancy is the patient's or physician's discontinuation of controller medication because of the concern about fetal effects. Both maternal and fetal outcome are optimized by good control of her asthma, and there are no data of adverse effects on the fetus associated with her controller medications.

4. A 28-year-old woman currently at 8 weeks' gestation in a first pregnancy presents with left leg pain. She was seen in a local emergency department, having recently returned from a car trip from Boston to Florida. She was advised to use nonsteroidal anti-inflammatory drugs and to elevate her leg. She has had extensive nausea and vomiting during her pregnancy. The findings of your examination are benign, with minimal swelling in the left calf. What should your recommendation be?

- A. Radiograph of left knee to ankle
- B. Doppler ultrasound of left leg to rule out deep venous thrombosis (DVT)
- C. Decrease exercise, especially aerobic classes
- D. Examine her for probable restless leg syndrome associated with pregnancy
- E. Encourage oral rehydration for her dehydration

Answer: B Pregnant patients are at an increased risk of thrombosis, beginning early in gestation. The hormonal effects leading to venodilation and stasis as well as pregnancy-related increase in coagulation activation are already present in this patient. Her dehydration further increases her hypercoagulability. In addition, more than 90% of DVT during pregnancy and the postpartum period occurs on the left side, so her pretest probability of this being DVT is higher than at baseline.

Ch / 240 **MENOPAUSE**

1. Which of the following case histories documents that the woman is in the early menopause transition?

- A. A 50-year-old woman complains of labile mood, forgetfulness, and loss of libido and reports that she missed a menstrual period last month.
- B. A 54-year-old woman reports that she has not had a menstrual period for a year and is having hot flashes.
- C. A 48-year-old smoker complains that she is having hot flashes and trouble sleeping and reports that she has missed three menstrual periods in the past year.
- D. A 48-year-old woman who is taking birth control pills reports gaining 10 pounds in the past year.
- E. A 60-year-old woman complains that she has been having hot flashes for 10 years since her menstrual periods stopped, and the hot flashes recur every time she tries to stop her estrogen treatment.

Answer: C A woman in her mid-40s to mid-50s who complains of classic hot flashes is likely to be in the menopause transition. The fact that the woman in C has missed three menstrual periods in the last year suggests that she is in the early menopause transition. The symptoms reported by the women described in A and D are not associated with the menopause transition. The women described in B and E have undergone menopause or are in the late menopause transition because they have not had a menstrual period for a year.

2. What evaluation is required for a 52-year-old woman who has missed six menstrual periods in the previous year and complains of hot flashes?

- A. Lateral vaginal wall pH
- B. A careful pelvic examination to evaluate for vaginal atrophy
- C. Serum follicle-stimulating hormone (FSH) level
- D. Review of medications and prior medical history
- E. Serum thyroid-stimulating hormone level

Answer: D A clear history of appropriate age (mid-40s to mid-50s), missing menstrual periods, and classic description of hot flashes with no other medical problems that might cause flushing (see Table 240-1) is diagnostic of menopause-related hot flashes, and no further evaluation is needed. There are no associated physical findings, and FSH levels may be normal in the early menopause transition. If the woman is not complaining of vaginal symptoms, a pelvic examination or vaginal wall pH measurement is not helpful.

3. What treatment would you recommend for a 50-year-old woman with mild hot flashes?

- A. Reassure her that the symptoms are likely to resolve in a few years.
- B. Suggest that she dress in layers and keep her bedroom cool.
- C. If there are no contraindications, offer low-dose (7.5 mg/day) paroxetine.
- D. If there are no contraindications, offer low-dose hormone therapy.
- E. All of the above

Answer: E Many women with mild hot flashes want to be reassured that they are indeed in the menopause transition and that this is a normal stage of reproductive life. These women are often not bothered enough by hot flashes to want treatment. However, some women are bothered and would like to try treatment to alleviate the hot flashes. In this situation, a nonhormonal drug such as paroxetine, 7.5 mg daily, or a low-dose estrogen, such as 0.025 mg estradiol (combined with a progestin if she has a uterus), is likely to provide adequate relief.

4. What treatment would you recommend for a 50-year-old woman with severe hot flashes that are interfering with her ability to work? She has not had a hysterectomy, and her only other medical problem is osteoarthritis, for which she takes a nonsteroidal anti-inflammatory drug.

- A. Reassurance that the symptoms are likely to resolve in a few years
- B. A nonhormonal drug, such as low-dose paroxetine 7.5 mg daily
- C. Bioidentical hormone therapy
- D. Standard-dose estrogen given daily, combined with a progestin given on the last 10 to 14 days of the month or half-dose progestin given daily
- E. Estradiol 0.5 mg given daily

Answer: D A woman with severe hot flashes is unlikely to obtain adequate relief with nonhormonal treatments. However, if she wishes to try these treatments before taking hormone therapy or there is a contraindication to hormone therapy, it would be appropriate to try a nonhormonal treatment such as paroxetine or escitalopram. A woman with a uterus should have a progestin added to estrogen therapy to avoid the increased risk of endometrial hyperplasia and cancer associated with unopposed estrogen therapy. This can be done by adding standard-dose progestin on days 10 to 14 of the month (or by using a sequential combination estrogen plus progestin pill) or by adding half-dose progestin daily (or using a combination estrogen plus progestin pill or transdermal patch). Hormone therapy options are provided in Table 240-2. The various types of estrogen and progestins are equally effective at equivalent doses. Some women prefer a patch, whereas others prefer a pill; both the oral and transdermal routes are effective.

5. What treatment would you recommend for a 65-year-old woman with severe vaginal dryness, itching, and dyspareunia?

- A. Reassurance that the symptoms are likely to resolve in a few years
- B. Use of a vaginal lubricant as needed for sexual intercourse
- C. Use of a vaginal moisturizer daily or three times per week
- D. Estrogen vaginal cream
- E. Estrogen vaginal ring

Answer: D or E The best answers are D and E. Reassurance is inappropriate, as unlike hot flashes, menopause-related vaginal symptoms generally do not resolve over time. The woman could try vaginal lubricants for sexual intercourse and a vaginal moisturizer such as Replens, but these are unlikely to provide adequate relief of symptoms. Low-dose topical estrogen applied to the vagina is the most effective treatment. Estrogen can be provided as a cream, vaginal tablet, or slow-release ring. Treatment options are provided in Table 240-3. If topical estrogens are used at low doses (two or three times per week as described in Table 240-3), added progestins are not required for women with a uterus.

1. A 25-year-old woman comes to the emergency department with a bruise to her left eye. She is accompanied by a woman whom she refers to as a friend. The patient explains that she was hit in the eye while playing baseball. The friend insists on remaining with the patient while the initial history is taken by the nurse. Which of the following is the most appropriate recommendation?
- A. The friend should be asked politely to leave during the history taking, which should include exploration about the possibility of intimate partner violence (IPV).
 - B. The patient should first be asked if she wants her friend to stay, and if she agrees, the patient can be asked about IPV.
 - C. The patient should be asked if the friend is a partner; if not, it is acceptable to proceed with exploration of IPV in the presence of the friend.
 - D. Because the patient is accompanied by a friend, it is important not to inquire about exposure to IPV because of confidentiality.
 - E. Because the patient has given a plausible explanation for the bruise to her eye and there is no evidence for universal screening, she should not be asked about exposure to IPV.

Answer: A The patient has an injury that is suggestive of exposure to IPV. It is important that she be asked privately about the nature of the injury. Such inquiry is a form of case finding, not universal screening.

2. A 17-year-old pregnant woman comes to the family physician's office to discuss her plans for the pregnancy. During the visit, she discloses that her 20-year-old boyfriend has twice threatened to hit her before she became pregnant. Which of the following is the most appropriate approach by the family physician?
- A. Ask the patient whether she has ever experienced any physical injury from her boyfriend; if not, advise her that they should attend couple counseling together.
 - B. Advise the patient that the risk will likely escalate during the pregnancy and she should leave the partner.
 - C. Give the patient the opportunity to discuss her concerns at a pace that is comfortable for her.
 - D. Advise the patient that this creates significant risk for her infant in the future, and it is not safe for her to remain in the relationship.
 - E. Explain to the patient that it is best to return another day when the appointment can be set aside to discuss the issue in more detail.

Answer: C The patient needs to be given the opportunity to discuss her concerns at a pace that is comfortable for her. The other responses could put the patient at risk (A) or are too directive (B and D) or not sufficiently responsive to the patient's needs (E).

3. A 56-year-old woman is a new patient in a family medicine practice. In her first consultation, she presents with a 16-year history of recurrent depression. In taking a comprehensive history, the family physician asks about any experience of abuse. She discloses that she has been frightened of her husband for years. He is extremely controlling and occasionally physically violent. What is the most appropriate initial response from the physician to this disclosure?
- A. Have you ever thought about packing your bags and leaving him?
 - B. Have you ever thought about going to couple counseling?
 - C. Is there something you could do differently so that he becomes less angry?
 - D. That must be very difficult for you; I can help you find support.
 - E. That sounds frightening; do you want me to have a word with him?

Answer: D The priority must be initial validation, empathizing with the patient and signaling that support is available. The other responses are too directive (A) or could increase risk to the patient (B and E) or are victim blaming (C).

4. A clinical team is developing a policy on IPV. It should include which of the following?
- A. A protocol for annual screening of all women patients for current abuse
 - B. A mandatory reporting requirement ensuring that the police are informed in all cases of serious assault
 - C. Recording of abuse in the medical record of the victim and the perpetrator
 - D. A training program on IPV for all clinical staff that includes a referral pathway to IPV advocacy support

Answer: D Training of clinicians is a prerequisite for an appropriate response to patients experiencing IPV, and a referral pathway to advocacy removes one of the barriers to the clinician's asking about abuse. The other responses are not based on evidence of effectiveness (A) or could increase the risk to the patient (B and C), also reducing the likelihood of disclosure to health care providers.

Ch / 243 **OSTEOPOROSIS**

1. A 60-year-old woman presents to her physician to discuss her recent bone density results and management options. She has treated hypertension and a history of atrial fibrillation, as well as rheumatoid arthritis, for which she takes infliximab. Family history is notable for a hip fracture in her mother after a fall at age 65 years. She drinks socially and does not smoke. Her physical examination is unremarkable, including only 1 inch of height loss from her young adult maximum. Her spine examination reveals normal curvature, no kyphosis, normal rib-pelvis distance of 3 fingerbreadths, and 0 fingerbreadth wall-occiput distance. Laboratory studies are normal, including 25(OH)D level. Dual-energy x-ray absorptiometry (DXA) bone density reveals lumbar spine, femoral neck, and total hip T scores of -2.5, -3.0, and -2.7, respectively. Her FRAX 10-year estimates of hip and major osteoporotic fracture are 5.6 and 29%, respectively. What is the best management recommendation for this woman?

- A. Calcium and vitamin D supplementation alone
- B. Hormone replacement therapy
- C. Raloxifene
- D. Oral bisphosphonate
- E. Denosumab

Answer: D This patient has osteoporosis based on T score at the lumbar spine and proximal femur. In addition, she has an absolute fracture risk that supports pharmacologic intervention on a cost-effectiveness basis. Oral bisphosphonates are effective and generally frontline therapy. Active use of immunosuppressive therapy increases her risk for infection, which was seen more frequently in denosumab-treated patients in randomized controlled trials. Her cardiovascular history increases her risk for stroke, which has been observed more frequently in raloxifene- and estrogen-treated patients. Finally, calcium and vitamin D are important adjuncts to her management but should not be considered adequate alone for fracture risk reduction in this woman.

2. A 65-year-old woman presents with 6 months of progressive lower extremity pain and describes difficulty ascending stairs because of pain and weakness. She also brings a recent outside DXA bone density test, which shows total hip T and Z scores of -4.5 and -2.5, respectively. She does not have a history of fragility fractures. Past medical history is notable for hypertension and long-standing irritable bowel syndrome. She takes 600 mg of calcium and 400 IU of vitamin D daily, but no other medications. Family history is negative for osteoporosis or parental hip fracture. She does not smoke or drink alcohol. Physical examination is notable for tenderness to palpation over the mid-tibia bilaterally. She also has a wide-based, nonantalgic gait. What is the next best choice for her skeletal management?

- A. Double her calcium and vitamin D daily intake.
- B. Measure serum 25(OH)D level.
- C. Start an oral bisphosphonate.
- D. Measure fasting serum C telopeptide level (CTx)
- E. Start teriparatide therapy.

Answer: B This patient has lower bone density than expected for age based on Z score of -2.0 or less. This suggests a secondary cause for low bone mineral density (BMD) besides menopause. Her clinical presentation is consistent with osteomalacia, which cannot be distinguished from osteoporosis based solely on BMD. In addition, the prevalence of vitamin D deficiency or insufficiency and established hip fracture efficacy warrant its identification and treatment as the next best step in patient management. The recommended increase in calcium and vitamin D would be insufficient to treat vitamin D deficiency-related osteomalacia in this woman, and bisphosphonate and teriparatide therapy would be inappropriate until the vitamin D deficiency is corrected. Finally, bone turnover markers cannot be used independently for diagnosis in patients with metabolic bone disease.

3. An 81-year-old man is admitted after a fall and low-impact fracture of the proximal femur. His history is notable for Parkinson's disease treated with dopamine agonist therapy. On physical examination, patient has a mild resting tremor while lying in bed. Laboratory investigations do not reveal secondary causes of osteoporosis, including a 25(OH)D level of 30 ng/mL and testosterone of 300 ng/dL. The patient has normal renal function and calcium. The patient undergoes successful operative repair. After discharge, the patient undergoes 4 weeks of inpatient rehabilitation. What is the most definitive choice for this patient's metabolic bone management?

- A. Start calcium and vitamin D supplementation.
- B. Increase dopamine agonist therapy for Parkinson's disease.
- C. Give zoledronic acid, 5 mg intravenously.
- D. Start testosterone replacement therapy.
- E. Prescribe ergocalciferol 50,000 IU once weekly.

Answer: C This gentleman has incurred a low trauma femur fracture, which greatly increases his risk for subsequent fractures. Furthermore, the fracture confers a mortality rate up to 30% within 1 year of the event. Zoledronic acid has been proved not only to reduce the risk for subsequent fracture but also to reduce mortality by 27%. Calcium and vitamin D are important adjuncts to treatment but not definitive. Given his level of 25(OH)D, additional antifracture and/or fall risk reduction would not be anticipated from pharmacologic vitamin D treatment. There is no evidence that testosterone treatment of either eugonadal or hypogonadal men reduces fracture risk. Finally, optimal management of his Parkinson's disease, which does not appear undertreated in this patient, might reduce his risk for falls but not his risk for fracture.

4. A 55-year-old white woman presents to her physician with intense mid-back pain after a fall onto her backside while walking. Her history is notable for a recent diagnosis of polymyalgia rheumatica, for which she has taken prednisone 10 mg daily for the last 6 months. She does have known osteopenia, with lumbar spine, femoral neck, and total hip T scores of -1.5 , -1.2 , and -0.8 , respectively. Physical examination is notable for tenderness to palpation and percussion over the lower thoracic spine. Plain films of the thoracolumbar spine reveal a new moderate (35%) anterior compression fracture at T11. Laboratory work-up, including 25(OH), is within normal limits. Other than continuing the calcium and vitamin D that the patient is currently taking, what is the most appropriate pharmacologic choice for treatment at this time?

- A. Vitamin D 50,000 IU once weekly
- B. Alendronate 70 mg once weekly
- C. Risedronate 150 mg once monthly
- D. Teriparatide 20 mcg subcutaneously daily
- E. Denosumab 60 mg subcutaneously every 6 months

Answer: D This woman presents with an acute vertebral fracture following a low trauma event. Her level of BMD is not osteoporotic, underscoring the independent contribution of glucocorticoids to fracture risk such that fractures may occur at a higher (i.e., better) level of BMD. The recent nature of her fracture further underscores the need for initiation of treatment now. There is no evidence that increasing this patient's vitamin D level will further reduce her risk for fracture. Denosumab will likely reduce her risk for subsequent fracture, although the association with infection and use of concurrent prednisone in this woman preclude its consideration at present. Alendronate and risedronate are approved for the prevention and treatment of glucocorticoid-induced osteoporosis (GIO). Despite this, teriparatide has been proved more effective than bisphosphonates in patients with GIO and is indicated for this woman, assuming she has no contraindications to treatment.

5. A 70-year-old man presents with acute, mid-back pain after lifting a bag of topsoil while gardening 1 week ago. His medical history is notable for known male hypogonadism due to mumps orchitis in his 20s, although he does not take testosterone because of severe benign prostatic hypertrophy. He does take 600 mg of calcium twice daily and 1000 IU of vitamin D once daily. On physical examination, he has tenderness to palpation and percussion over his mid-thoracic spine. Laboratory investigations are unrevealing, including a 25(OH) level of 45 ng/mL. DXA bone density study confirms osteoporosis with lumbar spine T score of -3.0, although femoral neck and total hip T scores are normal. Radiographs of the thoracic spine reveal a new severe (50%) biconcave compression fracture at T8 without apparent widening of the pedicles. In addition to prescribing alendronate, which of the following is best adjunct management for this patient?

- A. Analgesic therapy and referral to physical therapy for post-fracture consultation
- B. Prescription for a spinal brace that patient should wear for 6 months
- C. Percutaneous vertebroplasty
- D. Nasal calcitonin use for 1 year
- E. No additional interventions are required at this time.

Answer: A This gentleman has osteoporosis secondary to long-standing hypogonadism, exhibited by predominantly great bone density loss and deficit in cancellous bone (i.e., spine). He has incurred by definition a low-trauma fracture and is in need of a pharmacologic antifracture therapy (i.e., alendronate). Although he has significant pain that must be addressed, there is no evidence that conservative therapy with analgesics is inferior to vertebroplasty in regard to pain management. In addition, his radiographic findings do not suggest fracture instability that might benefit from vertebroplasty. Physical therapy is also helpful both short term as an adjunct to pain management and long term regarding modification of lifestyle and exercise to maximally reduce future fracture risk. A supportive spine brace may be used, although its use should be limited to only 4 to 6 weeks because of the necessary induction of paraspinal muscle weakness associated with long-term use. Similarly, nasal calcitonin may have some analgesic benefit in the acute, post-fracture period based on limited data, although there is no evidence of a long-term analgesic benefit with continued use of the drug.

1. Defective mineralization in osteomalacia is due to lack of one or more of the following except which one?

- A. Adequate calcium and phosphorus at the remodeling site
- B. Adequate amount of skeletal alkaline phosphatase
- C. Normal pH at the site of calcification
- D. Presence of a normal bone collagen matrix
- E. Adequate level of fluoride

Answer: E Fluoride is an inhibitor of mineralization. See Pathobiology.

2. The correct sequence of steps involving bone remodeling is represented by which one of the following?

- A. Reversal, activation, bone resorption by osteoclasts, osteoblast assembly and new bone formation
- B. Activation, bone resorption by osteoclasts, reversal phase, osteoblast assembly and new bone formation
- C. Bone resorption by osteoclasts, activation, osteoblast assembly and new bone formation, reversal
- D. Activation, osteoblast assembly and new bone formation, bone resorption by osteoclasts, reversal
- E. None of the above

Answer: B See Pathobiology.

3. All of the following may be signs or symptoms of osteomalacia except which one?

- A. Nonspecific and poorly localized bone pain
- B. Bone pain after sudden movements
- C. Fasciculations and absent reflexes
- D. Flat-footed waddling gait
- E. Muscle weakness

Answer: C See Clinical Manifestations.

4. Excessive osteoid due to osteomalacia can be reliably distinguished from that caused by increased bone turnover by which one of the following?

- A. Serum alkaline phosphatase
- B. Presence of pseudofractures
- C. Increased radionuclide on a bone scan
- D. Phosphate level
- E. Bone histomorphometry using tetracycline labels

Answer: E See Diagnosis.

5. A 30-year-old woman presents to her primary care physician with fatigue, generalized bone pains, weight loss, and a pruritic rash on her elbows and back. Laboratory studies show: hemoglobin 10 (male, 14-17 g/dL; female, 12-16 g/dL); serum iron 20 (60-160 µg/dL); serum calcium 8 (9-10.5 mg/dL). What is the next appropriate diagnostic test?

- A. Bone mineral density scan
- B. Hemoglobin electrophoresis
- C. Colonoscopy
- D. Antiendomysial immunoglobulin A antibodies
- E. Skin biopsy

Answer: D The patient has gluten enteropathy, which may occur even without gastrointestinal symptoms. See Treatment.

1. Which one of the following statements is true for the actions of parathyroid hormone (PTH)?

- A. Acts directly on renal, bone, and intestinal cells
- B. Acts directly on renal cells and indirectly on bone and intestinal cells
- C. Acts directly on renal and bone cells and indirectly on intestinal cells
- D. Has no direct actions on renal, bone, and intestinal cells
- E. Acts via a tyrosine kinase receptor

Answer: C PTH shares a receptor with PTH-related peptide (PTHrP), and this receptor is a member of the G protein-coupled receptor (GPCR) family. PTH/PTHrP receptors are expressed by kidney and bone cells, and PTH acts directly on renal and bone cells. PTH acts indirectly on intestinal cells to enhance calcium absorption as follows: PTH stimulates renal 1α -hydroxylase activity to promote synthesis of the active form of vitamin D (1,25-dihydroxyvitamin D), which then acts on the intestine to enhance calcium absorption.

2. Which of the following is not a cause of hypercalcemia?

- A. Granulomatous disorders
- B. PTH receptor loss-of-function mutation
- C. Autoimmunity
- D. Renal 1α -hydroxylase overactivity
- E. Myeloma

Answer: B PTH receptor loss-of-function mutations result in Blomstrand's chondrodysplasia, which is not associated with hypercalcemia. Instead, PTH receptor gain-of-function mutations that lead to Jansen's metaphyseal chondroplasia are associated with severe hypercalcemia. Granulomatous disorders, autoimmunity (e.g., autoantibodies to the calcium-sensing receptor), renal 1α -hydroxylase overactivity, and myeloma may all be associated with hypercalcemia.

3. Which of the following statements is not included as a recommendation for parathyroid surgery in asymptomatic primary hyperparathyroid patients?

- A. Serum calcium >10 mg/dL (0.25 mmol/L) above upper limit of normal
- B. Reduction in bone mineral density by T score ≤ -2.5
- C. Reduction in creatinine clearance below 60 mL/min
- D. Marked hypercalciuria (>400 mg per 24 hr, >9 mmol/L per 24 hr))
- E. Age <50 years

Answer: D Marked hypercalciuria (>400 mg per 24 hr, >9 mmol/L per 24 hr) was included as a recommendation for parathyroid surgery in asymptomatic primary hyperparathyroidism by the Second International Conference (2002), but not by the Third International Conference (2008). However, some physicians still regard marked hypercalciuria as an indication for parathyroid surgery.

4. Which of the following statements regarding parathyroid tumors in multiple endocrine neoplasia (MEN) syndrome is *false*?

- A. In MEN 1, parathyroid tumors occur with equal frequency in men and women.
- B. In MEN 2b and MEN 3, parathyroid tumors are a rare occurrence.
- C. In MEN 1, minimally invasive surgery is not a suitable approach because of the high occurrence of multiple parathyroid tumors.
- D. Patients with MEN 2a have a higher risk for developing parathyroid carcinomas.
- E. Parathyroid tumors occur in more than 95% of MEN 1 patients.

Answer: D MEN 1 is an autosomal dominant disorder, and this generally affects men and women equally. Parathyroid tumors are found in more than 95% of patients with MEN 1, who usually have multiple parathyroid tumors, and hence minimally invasive surgery is not recommended. Parathyroid

tumors rarely occur in patients with MEN 2b or MEN 3, and about 20% of MEN 2a patients will usually have parathyroid hyperplasia and not parathyroid carcinoma. However, patients with hyperparathyroidism with jaw tumors are at high risk for developing parathyroid carcinomas.

5. Which of the following is not a cause of hypocalcemia?

- A. Vitamin D–resistance disorders
- B. Secondary hyperparathyroidism
- C. Adrenal insufficiency
- D. Autoimmunity
- E. Acute pancreatitis

Answer: C Acute adrenal insufficiency is associated with hypercalcemia, not hypocalcemia.

Hypocalcemia typically occurs in patients with secondary hyperparathyroidism and in those with vitamin D–resistance disorders, and it may be found in patients with acute pancreatitis. In addition, autoimmune destruction of the parathyroids, resulting in hypoparathyroidism, or autoantibodies to the calcium-sensing receptor may be associated with hypocalcemia.

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MEDULLARY THYROID CARCINOMA

1. Sporadic medullary thyroid carcinomas (MTCs) without somatic *RET* mutations most commonly have which of the following?

- A. Somatic *RAS* mutations
- B. Germline *RET* mutations
- C. Somatic *BRAF* mutations
- D. No additional genetic mutations
- E. Gene fusions involving the *RET* protooncogene

Answer: A About half of patients with sporadic MTC have somatic *RET* mutations, and about 70% of sporadic MTCs with no somatic *RET* mutations have *HRAS*, *KRAS*, or rarely *NRAS* mutations. (Moura MM, Cavaco BM, Pinto AE, Leite V. High prevalence of RAS mutations in RET-negative sporadic medullary thyroid carcinomas. *J Clin Endocrinol Metab.* 2011;96: E863-868.)

2. Patients with MEN 2A who develop pheochromocytomas and hyperparathyroidism, in addition to MTC, most commonly have mutations in which codon?

- A. *RET* codon 620.
- B. *RET* codon 918
- C. *RET* codon 634
- E. *RET* codon 791
- E. *RET* codon 804

Answer: C There is a clear relationship between genotype and phenotype in patients with MEN 2A. Virtually all patients with this syndrome develop MTC, but the development of pheochromocytoma and hyperparathyroidism is highly variable, occurring much more often in patients with *RET* 634 codon mutations and much less frequently in patients with other *RET* codons mutations. (Wells SA Jr, Pacini F, Robinson BG, Santoro M. Multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma: an update. *J Clin Endocrinol Metab.* 2013;98:3149-3164.)

3. After thyroidectomy, the most reliable indicator of prognosis is which of the following?

- A. The specific *RET* or *RAS* mutation associated with the MTC
- B. The serum levels of calcitonin (CTN) and carcinoembryonic antigen (CEA) immediately postoperatively
- C. The rate at which serum CTN and CEA double
- D. The completeness of the thyroidectomy
- E. The gender of the patient

Answer: C The presence of an elevated serum CTN or CEA in the immediate postoperative period or soon thereafter is diagnostic of persistent or recurrent MTC. Although this determination is valuable, it is not as significant an indicator of prognosis as the rate at which serum levels of CTN and CEA double. Doubling times of less than 6 months for either CTN or CEA are a very poor prognostic sign. (Meijer JA, le Cessie S, van den Hout WB, et al. Calcitonin and carcinoembryonic antigen doubling times as prognostic factors in medullary thyroid carcinoma: a structured meta-analysis. *Clin Endocrinol.* 2010;72:534-542.)

4. In patients with MEN 2B where the *RET* mutation arises de novo, the mutated allele comes from which parent(s)?

- A. The mother
- B. The father
- C. Either parent
- D. Neither parent

Answer: B In patients with de novo MEN 2B, where neither parent expresses the characteristic phenotype associated with the disease, the mutated *RET* allele is virtually always inherited from the father. The average age of males who transmit the disease is significantly greater than the average age of all fathers. This appears to be due to a selective advantage acquired by the testis stem cells, which increases the mutation's frequency in the testis. (Choi SK, Yoon SR, Calabrese P, Arnheim N. Positive selection for new disease mutations in the human germline: evidence from the heritable cancer syndrome multiple endocrine neoplasia type 2B. *PLoS Genet.* 2012;8:e1002420.)

5. In patients with hereditary MTC, thyroidectomy should be performed within the first 5 years of life in which cases?

- A. All patients with a germline *RET* codon mutation
- B. Only patients with MEN 2B
- C. Patients with MEN 2A who have a germline *RET* codon 634 mutation and patients with MEN 2B
- D. Patients with a germline *RAS* mutation
- E. Patients who only have an elevated serum calcitonin level

Answer: C The published guidelines for managing patients with hereditary MTC all discuss the timing of thyroidectomy in children who have inherited a mutated *RET* allele. There is uniform agreement that thyroidectomy should be performed before 5 years of age in patients with *RET* mutations in codon 634, and as soon as the diagnosis is made in patients with MEN 2B, even in the first months of life. (Kloos RT, Eng C, Evans DB, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid.* 2009;19:565-612.)

1. A previously healthy 75-year-old man presents to his primary care physician with pain in the left hip that is worse on walking. Systematic enquiry is unremarkable, but examination reveals pain and a reduction in range of movement of the left hip. Radiography shows mixed osteosclerotic-osteolytic lesions in the right hemipelvis with expansion of the iliac bone. Osteophytes and joint space narrowing are observed in the left hip. Routine hematology, urea and electrolytes, calcium and phosphate, and liver function tests are normal, but alkaline phosphatase is raised at 200 μL (reference range, 40 to 125). Serum 25(OH)D is 35 nmol/L, parathyroid hormone is 7ng/L (normal, 2 to 12). What is the most likely cause of the hip pain?

- A. Paget disease of the pelvis
- B. Osteoarthritis of the hip
- C. Osteomalacia
- D. Osteoporosis
- E. Prostate cancer

Answer: B Osteoarthritis of the hip. Although the blood test results are consistent with Paget disease, the pain is localized to the noninvolved side of the pelvis. Although serum 25(OH)D is slightly reduced, osteomalacia is unlikely because this does not usually present with localized pain, and parathyroid is normal. Prostate cancer with bone metastases can cause osteosclerotic metastases, which can look similar to Paget disease on radiography, but the fact that he is clinically well makes this less likely.

2. A 47-year-old man with known Paget disease of the left tibia presents with pain localized to the anterior aspect of the affected tibia. On examination, there is mild deformity of the tibia on the left side, with warmth of the skin overlying the tibia. Hematology and biochemistry are normal, including alkaline phosphatase, which is 105 (reference range, 40 to 125). What is the most appropriate treatment?

- A. Paracetamol
- B. Surgical osteotomy of the tibia to correct the deformity
- C. Amitriptyline
- D. Intravenous zoledronic acid, 5 mg IV annually for 3 years
- E. Intravenous zoledronic acid, 5 mg IV

Answer: E A single infusion of zoledronic acid would be the most appropriate option. The pain is clearly localized to an affected site and is likely due to Paget disease, even though the alkaline phosphatase is normal, because there is warmth of the overlying skin. To give three infusions would be unnecessary and would represent overtreatment because the clinical effects of zoledronic acid usually last for several years in Paget disease. Osteotomy can be used to correct significant deformity but would not be indicated to treat pain in a patient with mild deformity. Both paracetamol and amitriptyline can be used to help pain control in Paget disease, but in this case it would be appropriate to first assess the response to bisphosphonate before progressing to other treatments.

3. A 62-year-old woman presents with a 5-year history of musculoskeletal pain affecting the low back region, both shoulders, and both hips, neck, and head. She reports that her father and older brother have a history of Paget disease. Routine hematology, urea and electrolytes, calcium and phosphate, and liver function tests are normal, but alkaline phosphatase is raised at 2350 μL (reference range, 40 to 125). A radiograph of the pelvis shows typical changes of Paget disease. What would be the most appropriate investigation to determine the extent of the disease?

- A. Magnetic resonance imaging (MRI) of the spine
- B. Computed tomography (CT) of the abdomen, chest, and pelvis
- C. Serum bone specific alkaline phosphatase
- D. Radionuclide bone scan.
- E. Radiograph of the skull, shoulders, and cervical spine

Answer: D Radionuclide bone scan. Bones that are affected by Paget disease typically show intense tracer uptake, allowing one to delineate the extent of involvement in a single test. Imaging with MRI or CT can be useful if complications of Paget disease are suspected, such as spinal stenosis or osteosarcoma, but are not as useful in determining the extent of the disease. Bone-specific alkaline phosphatase will provide information on whether the elevated alkaline phosphatase is of bony origin but will not provide information on disease extent. Although radiographs can detect Paget disease with reasonable sensitivity, one would need to perform a whole skeletal survey to evaluate the extent of the disease.

4. A 75-year-old man develops pain in the low back region that is gradually worsening and has started to radiate into the buttocks on walking. A lateral radiograph of the lumbar spine shows mixed osteosclerotic-osteolytic lesions in lumbar vertebrae 2, 3, and 4, with expansion of all three vertebrae. Routine hematology, urea and electrolytes, calcium and phosphate, and liver function tests are normal, but alkaline phosphatase is raised at 350 μL (reference range, 40 to 125). What further investigations would be useful in determining the cause of the pain?

- A. MRI of the lumbar spine
- B. Anteroposterior radiograph of the spine
- C. Radionuclide bone scan
- D. Serum procollagen 1N peptide (PINP)
- E. CT scan of the lumbar spine

Answer: A MRI of the lumbar spine would be the most appropriate test because the symptoms are suspicious of spinal stenosis, which is a known complication of Paget disease of the lumbar spine and caused by expansion of the affected bones with encroachment on the cauda equina. The anteroposterior radiograph would not be useful in identifying spinal stenosis. Although the CT scan could give information on narrowing of the lumbar canal, it does not provide detail on the soft tissues, which would be necessary to determine whether the cauda equina is being compromised. The bone scan may show evidence of Paget disease in the spine but would not provide information on cauda equina compression. Measurement of PINP would provide information on bone formation but would not be helpful in defining the cause of the pain.

5. A 54-year-old man falls and sustains an injury to his right ankle. A radiograph is taken to exclude a fracture. No evidence of fracture is found, but changes consistent with early Paget disease are noted affecting the upper part of the right tibia. On clinic review 6 weeks after the injury, the patient has fully recovered and is asymptomatic. Routine biochemistry and hematology are normal. What would be the most appropriate evidence-based treatment option for this patient?

- A. Prophylactic therapy with intravenous zoledronic acid every 3 years for the next 10 years to prevent progression of the disease.
- B. Prophylactic therapy with oral alendronate 70 mg once a week on a long-term basis to prevent progression of the disease.
- C. Close observation with repeat radiographs on an annual basis followed by zoledronic acid treatment, 5 mg IV, if the radiographs shows signs of progression.
- D. Surgical removal of the upper part of the tibia with total knee replacement.
- E. Observation at periodic intervals with initiation of bisphosphonate treatment should symptoms that are suggestive of Paget disease develop.

Answer: E There is currently no evidence that prophylactic therapy with any bisphosphonate can alter the natural history of the disease. Similarly, there is no evidence that prophylactic surgery would be helpful in this situation. The most appropriate option would be to keep the patient under review to look for the development of symptoms that might be attributable to the Paget disease and give treatment if these occur.

1. Which of the following young adults is most likely to suffer from hay fever, seasonal rhinoconjunctivitis, atopic eczema, and dermatitis?
 - A. Raised in a wealthy family with access to excellent preventive health care
 - B. Born, raised, and living on a farm
 - C. Grew up as a “sickly child” with multiple ear infections, upper respiratory tract infections, and other infections
 - D. During childhood, had a mother with active TB that was being treated at home “for a long time with pills”
 - E. Youngest of five children whose parents did not allow him to have childhood immunizations

Answer: A This question relates to the concept known as the hygiene hypothesis, which postulates that decreased microbial stimulation early in life may lead to delayed maturation of the immune system, which in turn results in an increased risk of allergic diseases later in life. Although the situation with asthma specifically appears to be more complex, other allergic diseases are more prevalent in individuals of high socioeconomic status, in first-born children compared with later siblings (especially in large families), in multiply immunized individuals, and in those free of mycobacterial disease. In contrast, children raised on farms are less likely to develop allergic disorders later in life, possibly because of their early exposure to diverse microbial environments in animal sheds, haylofts, harvesting, and other farm activities. See Epidemiology.

2. Which of the following symptoms is characteristic of an anaphylactic reaction?
 - A. Angioedema
 - B. Metallic taste
 - C. Abdominal pain
 - D. Sense of impending doom
 - E. All of the above

Answer: E Anaphylaxis, the most important and a potentially fatal allergic emergency, can be manifested with any single one or a combination of a wide variety of symptoms, including cutaneous (urticarial, angioedema, flushing), respiratory (stridor from laryngeal edema, wheezing), cardiovascular (hypotension, arrhythmia, extravascular fluid loss), gastrointestinal (vomiting, abdominal pain, diarrhea), or nonspecific symptoms (metallic taste in mouth, sense of impending doom). See Anaphylaxis under the History section of Diagnosis.

3. Diagnosis of a specific allergic disorder requires
 - A. No laboratory testing if the clinical history is characteristic
 - B. Increased serum level of total IgE
 - C. Increase in serum allergen-specific IgE
 - D. Increase in serum allergen-specific IgE coinciding with symptoms
 - E. Demonstration of dermatographism

Answer: D The presence of allergen-specific IgE antibody and a clear temporal correlation between exposure to allergen and the genesis of symptoms are required to conclude that a patient is allergic to a specific allergen. In the absence of symptoms, a positive test response for allergen-specific IgE alone is termed sensitization but not allergy. Total levels of IgE in serum may be normal in the presence of allergic disease, and therefore its measurement is rarely helpful in making a diagnosis. See Assessment of Total and Allergen-Specific Immunoglobulin IgE under Laboratory Evaluation.

4. A young woman is found unresponsive, lying on a sidewalk. She is brought to the emergency department, where she is resuscitated but found to be in respiratory failure, requiring intubation, and in shock. No previous history is known, and the cause of her shock is not clear. Which of the following tests can diagnose anaphylactic shock in this case?

- A. Increased serum IgE level
- B. Eosinophilia
- C. Increased serum tryptase level
- D. Histamine or methacholine challenge
- E. None of the above is useful without a clinical history

Answer: C The quantification of tryptase, a mast cell–specific protease with a half-life of 2 hours, can be helpful to diagnose anaphylaxis if it is performed on serum or plasma obtained within hours of a systemic reaction with associated hypotension. Histamine or methacholine challenge is not even feasible under these circumstances. The other blood tests are not sufficiently sensitive or specific.

5. In the evaluation of a patient with frequent infections for a possible immunodeficiency disorder, her history reveals late separation of the umbilical cord at birth, recurrent and persistent gingivitis and periodontitis, and recurrent bacterial infections with granuloma formation. Which of the following categories of immunologic disorders is she most likely to have?

- A. Cellular immune defect
- B. Neutrophil dysfunction
- C. Complement deficiency
- D. IgA deficiency
- E. Severe variable immunodeficiency

Answer: B These findings along with persistent neutrophilic leukocytosis are characteristic of disorders of neutrophil dysfunction. Infections in individuals with cellular immune defects are more likely to be viral, fungal, or parasitic (opportunistic) in etiology, and they may also have malabsorption and diarrhea. Complement deficiencies are typically associated with recurrent bacterial infections, especially neisserial infections, and rheumatic diseases like systemic lupus erythematosus. IgA deficiency and other antibody deficiency disorders are characterized by recurrent respiratory infections with encapsulated organisms.

*Note: Dr. Wasserman had no role in the development of these questions.

1. A 30-year-old man has had episodes of chronic diarrhea for several years. He is thin and has had a 10-pound weight loss during the previous year. He has had an extensive gastrointestinal evaluation for Crohn disease, but the biopsies were inconclusive; however, villous blunting and a lack of plasma cells were noted in the intestinal mucosa. Which of the following might be appropriate?

- A. Test for anti-endomysial antibodies.
- B. Treat with steroid.
- C. Test for serum IgG, IgA, and IgM.
- D. Test for stool parasite.
- E. Order computed tomography of the abdomen with contrast enhancement.

Answer: C Loss of plasma cells in the gastrointestinal mucosa is a signal that there is a profound lack of B-cell development. This is a characteristic in common variable immune deficiency in general in those with or without gastrointestinal disease and would be expected to be associated with low serum levels of IgG, IgA, and IgM. Whereas celiac disease, for which testing for anti-endomysial antibodies would be sensitive and specific, is also characterized by villous atrophy, intestinal biopsy in this disease demonstrates increased lymphocyte and plasma cell infiltration, not absence of plasma cells.

2. A 64-year-old man goes to an allergist with chronic sinusitis for 3 years but no other significant illnesses aside from onychomycosis of several fingernails. Skin test results for allergy to aeroallergens are negative, and the allergist tests quantitative immunoglobulins. These show an IgG level of 160 mg/dL (normal, 700 to 1600 mg/dL), IgA level of 7 mg/dL (normal, 40 to 250 mg/dL), and IgM level of 12 mg/dL (normal, 50 to 300 mg/dL). Which of the following is the next step?

- A. Give an antifungal cream.
- B. Test serum Ig.
- C. Culture the sinuses.
- D. Order computed tomography of the chest.
- E. Request a bone marrow examination.

Answer: D This is likely to be Good syndrome, thymoma with hypogammaglobulinemia (or agammaglobulinemia). The main characteristics are the later onset and the observation of nail fungus. For diagnosis of this syndrome, computed tomography (or magnetic resonance imaging) of the chest is needed. The loss of antibody will require immunoglobulin replacement.

3. A 21-year-old woman comes to the emergency department with 4 days of chest pain, some blood-stained sputum, and a low-grade fever for 2 days. Her medical history includes severe eczema since infancy, an abscess on her buttock that required in-hospital surgical drainage, and a wrist fracture on closing a file cabinet. Aside from the fairly severe eczema, she does not appear ill; her white blood cell count is 9400 with 70% neutrophils and 10% eosinophils. Which of the following is the next step?

- A. It is likely a viral syndrome and she can be discharged.
- B. Give her a prescription for an antibiotic for 5 days.
- C. Get a chest radiograph.
- D. Treat the eczema more aggressively.
- E. Evaluate her for asthma with pulmonary function tests.

Answer: C With the clinical history, this may be hyperimmunoglobulin E syndrome (HIES). Pneumonias in HIES often lead to fewer clinical signals of toxicity; her past history of eczema since infancy, a significant abscess requiring drainage, and a fracture with minimal trauma suggest this diagnosis. A white blood cell count may not show neutrophilia, but eosinophilia is common. She needs a chest radiograph and, if it is abnormal, computed tomography to demonstrate the infection. At least 80% of HIES patients have had one or more pneumonias, often with mild symptoms; these lead to cysts and lung cavities.

4. A 29-year-old software designer was referred for evaluation of hypogammaglobulinemia. Recent evaluation for an enlarged spleen had revealed low serum levels of all immunoglobulins, including an IgG level of 251 mg/dL, IgA level 10 mg/dL, and IgM level 39 mg/dL. At the age of 15 years, he was febrile, anemic, and thrombocytopenic and developed splenomegaly and lymphadenopathy. He had a bone marrow that showed normal hematopoiesis, but the stain for Epstein-Barr virus (EBV)– encoded RNA (EBER) was positive. He was diagnosed with mononucleosis and recovered. His complete blood count is normal. Which of the following should be considered?

- A. HIV test
- B. Bone marrow examination
- C. Monospot
- D. Protein loss in the intestinal tract
- E. X-linked lymphoproliferative disease

Answer: E The X-linked proliferative disorder (XLP), due to mutations of the X-linked gene *SAP*, leads to a significant infection with EBV with lymphoproliferation, progressive but variable hypogammaglobulinemia, and, in some, lymphoma. This is the most common genetic disease leading to loss of control of EBV.

5. JF is a 27-year-old man who is referred because of the possibility of food allergy. For the past 5 years, he has had recurrent episodes of abdominal pain with nausea and vomiting and has concluded that he must be allergic to a common food ingredient. On one occasion, he had such severe abdominal pain that he went to the emergency department, where acute food poisoning and appendicitis were excluded. His father had a long history of “colitis” with intermittent abdominal pain and diarrhea. Which of the following tests might be helpful?

- A. Serum tryptase
- B. Serum C4
- C. Total hemolytic complement
- D. Computed tomography of abdomen with contrast enhancement
- E. Serum Ig

Answer: B With the severity of the pain and family history of a first-degree relative with an unexplained but somewhat similar abdominal pain, a C1 inhibitor defect is possible. The abdominal pain may be due to angioedema of the intestine. The best screening test would be serum C4, and if the level is low, one would proceed to test the C1 inhibitor protein and function.

1. A patient presents with a chief complaint of recurrent, protracted headaches that occur bilaterally in a maxillary distribution and are associated with nasal congestion and ocular tearing. These episodes occur spontaneously throughout the year. The most common cause of this condition is

- A. Allergic rhinitis
- B. Chronic sinusitis
- C. Migraine
- D. Nasal polyps
- E. Rebound headache

Answer: C The most common cause of “sinus” headache is migraine. Whereas acute sinusitis is often painful, chronic sinusitis is virtually never a source of pain. Migraines routinely occur in a maxillary distribution, are often bilateral, and often are inappropriately ascribed to sinusitis when they are associated with vasomotor symptoms such as nasal congestion and ocular tearing. Allergic rhinitis may trigger migraines and acute sinusitis but by itself would be an unusual cause of headaches. Nasal

polyps do not produce pain. Rebound headaches most commonly occur in the setting of caffeine or short-acting nonsteroidal anti-inflammatory drugs.

2. A 55-year-old woman presents with a chief complaint of continuous nasal congestion and posterior pharyngeal drainage. Symptoms are present year-round and interfere with her sleep and quality of life. Blood tests demonstrate specific IgE to cottonwood trees, *Alternaria*, and ragweed. The most likely explanation for this syndrome is

- A. Allergic rhinitis
- B. Chronic sinusitis
- C. Atypical migraine
- D. Nonallergic rhinitis
- E. Nasal polyps

Answer: D Nonallergic rhinitis most often is manifested with the combination of nasal congestion and posterior pharyngeal drainage. The absence of typical allergy symptoms of paroxysmal sneezing, pruritus, clear anterior secretions, and concomitant allergic conjunctivitis argues against allergic rhinitis as a cause. Allergic sensitization (presence of specific IgE by blood or skin testing) is common, is often not associated with symptoms on natural exposure, and therefore should not by itself be used to diagnose an allergic disease. In addition, the absence of sensitization to perennial allergens that can explain a year-round syndrome rules out an allergic etiology in this case. Whereas chronic sinusitis (with or without associated nasal polyps) can produce similar symptoms, these patients typically have additional complaints, such as “pressure” or “fullness” in a sinus distribution and reduced sense of smell. Migraines are episodic and are usually associated with headaches.

3. A 21-year-old patient presents with allergic rhinitis each spring, lasting continuously from early March through the end of June, that is associated with numerous pollen sensitizations. The most effective therapeutic intervention for this patient would be

- A. Oral antihistamines
- B. Intranasal cromolyn
- C. Intranasal corticosteroids
- D. Leukotriene modifiers
- E. Immunotherapy

Answer: C Intranasal corticosteroids are the most effective treatment for allergic rhinitis and are compellingly superior to antihistamines, leukotriene modifiers, and cromolyn in well-performed trials. Antihistamines are effective in mild intermittent disease, but once symptoms persist for more than a few days or weeks, they may prove little better than a placebo. Cromolyn and leukotriene modifiers are not as effective as corticosteroids. Immunotherapy may be effective, especially for grass pollen. It may be difficult to treat the patient for all of the pollinating trees present in her environment. In general, however, immunotherapy is reserved for patients who fail to respond to pharmacologic treatments.

4. A college student presents with a chief complaint of seasonal allergies that occur every year in late spring (May-June). Of the following, which is the most likely allergen explaining this history?

- A. Birch pollen
- B. Timothy grass pollen
- C. Ragweed pollen
- D. Dust mite (*Dermatophagoides pteronyssinus*)
- E. *Alternaria*

Answer: B Early spring allergic rhinitis is triggered by trees. Grasses pollinate in late spring and are what is driving this patient’s symptoms. Ragweed pollinates in late summer and autumn. *Alternaria* is an outdoor mold that is also particularly prevalent in the autumn. Whereas dust mites are often con-

sidered a perennial allergen, they are particularly active during periods of high humidity and as such often present as “seasonal” allergens with worse symptoms in the summer.

5. Left untreated, allergic rhinitis may contribute to the development of which of the following medical conditions?

- A. Benign nasal tumors
- B. Atypical migraines
- C. Eosinophilic granuloma (Langerhans cell histiocytosis)
- D. Eosinophilic esophagitis
- E. Chronic inflammatory (noneosinophilic) sinusitis

Answer: E Chronic rhinitis of any cause, including allergic rhinitis, occludes the sinus ostia. This can lead to frequent, persistent sinus infections and ultimately the remodeling of sinus tissue that characterizes chronic inflammatory sinusitis. Chronic sinusitis may be associated with extrusion of sinus tissue into the nasal air space, a condition referred to as nasal polyps. However, neither chronic sinusitis nor persistent allergic rhinitis produces nasal tumors. Similarly, allergic rhinitis produces a local (nasal) eosinophilic inflammatory process but not either eosinophilic esophagitis or eosinophilic granuloma. Although allergic rhinitis may trigger a migraine, it is not a cause of headaches, atypical or otherwise.

Ch / 252

URTICARIA AND ANGIOEDEMA

1. A 27-year-old woman wakes up with hives and appears in your office the same day for an urgent visit. On examination, she is not in acute distress but has multiple raised pruritic papules that blanch. The first medication you should prescribe is

- A. First-generation type 1 antihistamine
- B. Second-generation type 1 antihistamine
- C. Type 2 antihistamine
- D. Leukotriene pathway inhibitor
- E. Corticosteroid

Answer: B Second-generation type 1 antihistamines (cetirizine, fexofenadine, and loratadine) are better tolerated than the first-generation type 1 antihistamines. Often, the first generation antihistamines (e.g., diphenhydramine) are prescribed for breakthrough symptoms.

2. A 45-year-old man has had hives daily for 8 weeks. A combination of antihistamines (types 1 and 2) at high doses plus prednisone 20 mg daily controls the hives. What is the next step?

- A. Perform extensive testing to discover the offending food.
- B. Continue prednisone after documenting a discussion of possible side effects.
- C. Explain the importance of adherence to prescribed medications.
- D. Discuss adding an immunomodulatory drug.
- E. Initiate a work-up for systemic lupus erythematosus.

Answer: D This patient has failed to respond to conservative medical management. Chronic urticaria is a life-altering disease, and chronic steroid use is often associated with significant side effects. Current literature suggests that some immunomodulatory drugs, such as cyclosporine, can result in remission of the disease.

3. A 20-year-old man appears in your emergency department with acute abdominal pain. He has presented in this way in the past, without a definitive diagnosis. Examination now reveals a tender, swollen abdomen without bowel sounds. What is your next step?

- A. Laparotomy
- B. Appendectomy
- C. Narcotics
- D. Discharge secondary to malingering
- E. Take a detailed personal and family history

Answer: E Attacks of abdominal angioedema in patients with hereditary angioedema can mimic an acute abdomen. Also, these patients often seek pain relief and are incorrectly labeled “drug seeking.” A detailed personal and family history may reveal a pattern of swelling of the bowels or other parts of the body in either the patient or his immediate relatives. This will lead to appropriate laboratory studies and medical management.

4. A 50-year-old man carries the diagnosis of hereditary angioedema. He has been intubated twice and has minor episodes of swelling monthly. A trial of an attenuated androgen resulted in severe acne. Therapeutic options at this time include

- A. C1 INH twice weekly
- B. On-demand C1 inhibitor
- C. On-demand icatibant
- D. On-demand ecallantide
- E. All of the above

Answer: E All of these options are possible. Patients now have multiple options for management of hereditary angioedema, and these should be instituted on the basis of the needs of each patient.

5. A 10-year-old girl presents with a history of a hive-like rash that occurs when she is exposed to cold weather. Further questioning reveals that this is sometimes associated with myalgias and arthralgias and that several first-degree relatives have similar complaints. What is the most likely diagnosis?

- A. Chronic spontaneous urticaria
- B. Cholinergic urticaria
- C. Familial cold urticaria
- D. Familial cold autoinflammatory syndrome
- E. Systemic lupus erythematosus

Answer: D This uncommon disorder is often mistaken for familial cold urticaria, another unusual disease, and must be differentiated from common conditions such as chronic urticaria and systemic lupus erythematosus.

Ch / 253 **SYSTEMIC ANAPHYLAXIS, FOOD ALLERGY, AND INSECT STING ALLERGY**

1. In adults, which of the following triggers of anaphylaxis accounts for the most deaths?

- A. Peanuts
- B. Latex
- C. Penicillin
- D. Hymenoptera venom
- E. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs)

Answer: D The most common cause of anaphylactic death reported in adults is due to stings from insects, whereas in children, food allergic reactions may be more common. Adults who have experienced anaphylaxis to an insect sting in the past should be evaluated by an allergist for current

sensitivity and risk factors for severe anaphylaxis and encouraged to undergo venom immunotherapy as clinically appropriate, which can reduce the risk for severe anaphylaxis to future stings by more than 95%. The prevalence of latex allergy in general and latex-triggered anaphylaxis in particular seem to be declining now that powdered latex gloves have been removed from medical centers and latex-free products are available for almost any procedure. Medical centers and patients generally do a good job of avoiding penicillin exposure in penicillin-allergic patients, and alternatives to penicillins are available for most infections. Cardiovascular reactions associated with aspirin and NSAIDs that can mimic allergen-induced systemic anaphylaxis are, in most cases, pharmacologically (not immunoglobulin E [IgE]) mediated.

2. An anaphylactic reaction in a 45 year-old living in Virginia that occurs 3 to 6 hours after eating dinner is most likely due to which one of the following allergens?

- A. Bovine serum albumin in beef
- B. Tropomyosin protein in shrimp
- C. Alpha-gal carbohydrate in veal
- D. Penicillin in pork
- E. Melon in salad

Answer: C Particularly in the Southeastern and Mid-Atlantic states, perhaps due to exposure and sensitization to alpha-gal during Lone Star tick bites, IgE antibodies form against this antigen. Sensitized individuals can exhibit delayed urticarial or anaphylactic responses 3 to 6 hours after eating red meats, presumably because they do not react to monovalent alpha-gal-conjugated proteins in the meat soon after ingestion, but instead require several hours for this alpha-gal to be processed and form polyvalent, haptenized antigens. Interestingly, skin testing to a beef allergen extract is typically positive with sensitivity to protein allergens but negative with sensitivity to only alpha-gal, whereas in vitro testing of serum for allergen-specific IgE is positive in both cases. Anaphylactic reactions to protein allergens such as bovine serum albumin or tropomyosin occur acutely, generally within an hour of ingestion. Penicillin in beef or pork from penicillin-fed animals can cause anaphylaxis in penicillin-sensitive patients, but is uncommon and does so in less than an hour after ingestion. Individuals with pollen allergies may have pollen-specific IgE cross-reacting to certain food allergens, such as ragweed with melon, typically causing immediate-onset pruritus, irritation, and swelling around the mouth ("oral allergy syndrome").

3. Which of the following drugs is likely to activate mast cells on first exposure?

- A. Vancomycin
- B. Penicillin
- C. Phenytoin
- D. Bactrim

Answer: A Vancomycin directly activates mast cells on first and subsequent exposures, without involving the IgE-FcεRI pathway, but instead activating a G protein-coupled receptor. When peak levels of vancomycin are modest, red man syndrome results; hypotensive anaphylaxis can occur if the drug is infused too rapidly. Penicillin, phenytoin, and Bactrim (sulfamethoxazole and trimethoprim) can each haptenize proteins, elicit an IgE antibody response during a sensitization period, and then cause anaphylaxis with a subsequent exposure.

4. Mastocytosis, a clonal mast cell disorder that increases the risk for anaphylaxis, should be suspected if which of the following is elevated in serum taken from a patient at a time when their medical problem is clinically quiescent?

- A. Bradykinin
- B. Tryptase
- C. Serotonin
- D. Complement C5a
- E. Catecholamines and metanephrines

Answer: B Serotonin is not abundantly produced by mast cells. Bradykinin, generated extracellularly from kininogen precursors, also is not generated by mastocytosis patients during nonacute time periods. C5a is generated from C5 by proteases, typically by C5 convertases generated during activation of the complement pathways, and also by certain noncomplement pathway proteases, but is not generated during times when mastocytosis is clinically quiescent. Flushing syndromes like pheochromocytoma, which produces catecholamines and metanephrines, are only in the differential diagnosis to be distinguished from anaphylaxis. On the other hand, α - and β -protryptases are spontaneously released by mast cells at rest. Consequently, tryptase levels in serum, detecting both mature and protryptases and reflecting the increased mast cell burden and abnormal mast cell phenotype of mastocytosis mast cells, are typically elevated during nonacute periods of disease.

5. In the absence of exposure to a known allergen, the diagnosis and treatment of anaphylaxis should be most strongly considered in a patient who presents with the acute onset of which of the following signs or symptoms?

- A. Vomiting and diarrhea
- B. Abdominal pain
- C. Flushing and diarrhea
- D. Hypotension
- E. Urticaria and wheezing

Answer: E Acute onset of cutaneous signs of immediate hypersensitivity along with either hypotension or respiratory compromise in the apparent absence of allergen exposure; rapid onset of hypersensitivity signs involving at least two organs from among cutaneous, gastrointestinal, respiratory, and cardiovascular systems after exposure to a likely allergen; or rapid onset of hypotension after exposure to a known allergen can be used to diagnose systemic anaphylaxis in real time. In the scenario presented, lacking exposure to a known allergen, answers A and B only involve one organ system, C does not exhibit hypotension or respiratory signs, and D lacks cutaneous signs.

Ch / 254 **DRUG ALLERGY**

1. Which of the following drugs is *most* likely to cause drug hypersensitivity?

- A. Murine monoclonal anti-CD3 antibody
- B. Human insulin
- C. Chimeric monoclonal anti-CD20 antibody
- D. Humanized tumor necrosis factor antibody
- E. Human tumor necrosis factor antibody

Answer: A Biologic proteins from most to least allergenic are murine, chimeric, humanized, and finally fully human protein. Even fully human proteins like human insulin or fully human anti-tumor necrosis factor can cause hypersensitivity. However, the most likely protein to cause drug allergy is the most foreign protein, that is, a murine protein. (See Pathobiology.)

2. Which of the following clinical characteristics is *least* concerning for a serious cutaneous adverse reaction (SCAR) to a drug?

- A. Blistering lesions
- B. Painful lesions
- C. Pruritic lesions
- D. Pustular lesions

Answer: C Some features of SCARs that distinguish them from nonserious cutaneous reactions include involvement of other organs (e.g., liver, kidneys); fever; eosinophilia; mucosal involvement; and lesions that are painful, blistering, or pustular. Pruritus is not a distinguishing feature.

3. A patient taking multiple medications develops acute interstitial nephritis with normal findings on skin examination. Which of the listed drugs is the most likely culprit?

- A. Propranolol
- B. Phenytoin
- C. Colchicine
- D. Ampicillin

Answer: D Although most drug reactions include cutaneous manifestations, some only involve other organ systems, for example, pulmonary infiltrates with eosinophilia, hepatitis, and acute interstitial nephritis. Drugs that have been described to cause acute interstitial nephritis in the absence of cutaneous involvement include sulfonamides, nonsteroidal anti-inflammatory drugs, and penicillins like ampicillin and methicillin.

4. HLA genotyping has been useful in identifying individuals at increased risk of hypersensitivity to which of the following drugs?

- A. Amoxicillin
- B. Minocycline
- C. Ganciclovir
- D. Abacavir

Answer: D Human leukocyte antigen (HLA) genotyping can reportedly identify individuals who are at increased risk for drug hypersensitivity. For example, individuals with HLA-B*5701 are at greater risk for a drug hypersensitivity reaction to abacavir, an HIV transcriptase inhibitor. At many centers, abacavir is prescribed only after the HLA genotype is determined not to be HLA-B*5701.

5. Among the following, what is the *most* significant risk factor for drug allergy?

- A. Male sex
- B. HIV infection
- C. Atopy
- D. HLA-B27 genotype

Answer: B Drug-related rashes have been estimated to be 100 times more common in HIV-positive patients than in the general population. The reasons for this are not clear but are likely to be multifactorial and include changes in drug metabolism, oxidative stress, cytokine profiles, and immune hyperactivation. (See section Risk Factors under Epidemiology.)

1. Which of the following markers is aberrantly expressed by mast cells in patients with systemic mastocytosis?

- A. CD25
- B. CD117 (Kit)
- C. High-affinity IgE receptor
- D. CD45

Answer: A CD25 (alpha chain of the interleukin-2 receptor) is aberrantly expressed and is a sensitive diagnostic marker in systemic mastocytosis. All others are expressed by both normal and pathologic mast cells. (Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res.* 2001;25:603-625.)

2. A 25-year-old woman has recently been diagnosed with systemic mastocytosis by a bone marrow biopsy. There was no other hematologic disease noted. She experiences pruritus of the skin in hot weather and occasional abdominal cramping but is otherwise asymptomatic. *KIT* mutational analysis reveals the D816V mutation in bone marrow. Which of the following is the most appropriate treatment?

- A. Imatinib
- B. H1 and H2 antihistamines
- C. Prednisone
- D. Interferon alfa
- E. Bone marrow transplantation

Answer: B This patient has indolent systemic mastocytosis and should be treated symptomatically. Cyto-reductive therapies such as interferon alfa are indicated in patients with aggressive mastocytosis. The patient is not a candidate for imatinib because of indolent disease and presence of D816V *KIT* mutation. The patient's symptoms do not warrant bone marrow transplantation or use of systemic glucocorticoids, which are associated with long-term adverse effects. (Valent P, Akin C, Escribano L, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations, and response criteria. *Eur J Clin Invest.* 2007;37:435-453.)

3. A 35-year-old farmer with a 10-year history of mastocytosis who is otherwise healthy has recently experienced anaphylaxis with brief loss of consciousness after being stung by a honeybee. Allergy skin testing confirmed honeybee allergy. What is the most appropriate next step in management of honeybee allergy in this patient?

- A. Venom immunotherapy is not recommended because of increased risk of reactions to immunotherapy due to mastocytosis.
- B. Recommend venom immunotherapy for 5 years.
- C. Recommend venom immunotherapy indefinitely.
- D. Confirm skin test results by blood testing before recommending immunotherapy.

Answer: C Patients with mastocytosis are at increased risk for life-threatening reactions to hymenoptera stings. Fatalities have been reported in patients after discontinuation of venom immunotherapy. Therefore, most experts recommend immunotherapy when IgE-mediated sensitization is found by either skin or blood testing in these patients. Whereas the patients are also at increased risk of having a systemic reaction during immunotherapy, the risk-benefit ratio is often considered favorable to initiate immunotherapy. The patients should always continue to carry a self-injectable epinephrine as the protection is lower than for those without mastocytosis. (Niedoszytko M, de Monchy J, van Doormaal JJ, et al. Mastocytosis and insect venom allergy: diagnosis, safety and efficacy of venom immunotherapy. *Allergy.* 2009;64:1237-1245; and Alvarez-Twose I, Bonadonna P, Matito A, et al. Systemic mastocytosis as a risk factor for severe Hymenoptera sting-induced anaphylaxis. *J Allergy Clin Immunol.* 2013;131:614-615.)

4. Which of the following patients is a candidate for therapy with imatinib?

- A. 30-year-old with adult-onset indolent systemic mastocytosis with D816V *KIT* mutation who remains symptomatic despite symptomatic therapy
- B. 30-year-old with adult-onset systemic mastocytosis with occasional symptoms on symptomatic therapy; peripheral blood analysis negative for D816V *KIT* mutation
- C. 60-year-old with systemic mastocytosis, splenomegaly, and pancytopenias; peripheral blood and bone marrow positive for D816V *KIT* mutation
- D. 40-year-old with childhood-onset cutaneous mastocytosis that persisted into adulthood; patient recently developed progressive splenomegaly and anemia; mutational analysis of bone marrow shows an exon 8 *KIT* mutation

Answer: D Patients with D816V *KIT* mutation regardless of the category of mastocytosis are resistant to therapy with imatinib. Patients with cutaneous or indolent systemic mastocytosis with symptoms manageable by symptomatic therapy are not candidates for cytoreductive therapy regardless of the mutational status. Patients with well-differentiated systemic mastocytosis without codon 816 (exon 17) *KIT* mutations have a high likelihood of response to imatinib. (Akin C, Fumo G, Yavuz AS, et al. A novel form of mastocytosis associated with a transmembrane c-kit mutation and response to imatinib. *Blood*. 2004;103:3222-3225.)

5. Which of the following mast cell mediator measurements raises the greatest suspicion for mastocytosis?

- A. Tryptase level of 50 ng/mL in a patient with perioperative anaphylaxis, obtained 1 hour after the event
- B. Baseline tryptase level of 90 ng/mL in a patient who experiences recurrent anaphylactic episodes of unclear etiology
- C. Elevated urinary *N*-methylhistamine in a patient with recurrent unexplained flushing
- D. Elevated urinary prostaglandin D2 in a patient with chronic diarrhea and osteoporosis

Answer: B Urinary metabolites of mast cell mediators are neither more sensitive nor more specific than measurement of baseline tryptase in diagnosis of systemic mastocytosis. Tryptase levels increase (usually within 4 hours) after an anaphylactic event regardless of whether it is associated with mastocytosis. Some patients with recurrent unexplained anaphylaxis who may have been previously diagnosed with idiopathic anaphylaxis may have mastocytosis as an underlying disorder (especially if the anaphylactic episodes involve hypotension and syncope rather than urticaria or angioedema). The diagnosis should be confirmed by a bone marrow biopsy in the patient in option D. (Akin C, Scott LM, Kocabas CN, et al. Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with “idiopathic” anaphylaxis. *Blood*. 2007;110:2331-2333; and Akin C, Metcalfe DD. Surrogate markers of disease in mastocytosis. *Int Arch Allergy Immunol*. 2002;127: 133-136.)

1. On physical examination, which of the following categories of rheumatic diseases, when active, is *not* typically associated with inflammatory signs of synovitis?

- A. Systemic autoimmune diseases
- B. Degenerative diseases of bones and joints
- C. Pain syndromes
- D. Seronegative spondyloarthropathies
- E. By definition, they are all associated with synovitis.

Answer: C Signs of synovial inflammation (synovitis), including erythema, warmth, and swelling, are typically not found in the pain disorders like fibromyalgia, reflex sympathetic dystrophy, adhesive capsulitis, and regional myofascial pain syndromes. It is important to distinguish between *arthralgia*,

which is subjective joint pain without objective signs, and *arthritis*, in which pain is associated with objective signs of tenderness, swelling, and warmth (synovitis); the latter is sometimes also associated with deformity or limitation of movement.

2. A 65-year-old woman presents with complaints of increasing pain in her fingers and hands. She states that she has morning stiffness in those regions that tends to resolve within 10 to 15 minutes after start of activity. There are no other rheumatic or systemic symptoms and physical examination of the hands is completely normal. Which of the following is the most likely clinical diagnosis?

- A. Osteoarthritis
- B. Rheumatoid arthritis
- C. Fibromyalgia
- D. Scleroderma/systemic sclerosis
- E. Systemic lupus erythematosus (SLE)

Answer: A Morning stiffness that resolves in 10 to 15 minutes is most characteristic of osteoarthritis. The morning stiffness of rheumatoid arthritis and other inflammatory rheumatic diseases typically lasts longer: at least 1 hour and even for much of the day. Hand involvement with scleroderma/SSc is characteristically associated with initial swelling of the digits, then progressing to skin tightness, which was not observed in this patient. Fibromyalgia involves widespread body pain of both sides, including upper and lower extremities, back and neck. This would be an unusual age for presentation with SLE, which typically begins in women in the age range of 15 to 45 years.

3. Which of the following would *not* be considered an important epidemiologic factor in the differential diagnosis of a patient with rheumatic disease?

- A. Occupation and recreational activities
- B. Age and gender
- C. Concomitant medication use
- D. Family history
- E. Global geographic origin

Answer: E Connective tissue diseases are ubiquitous around the world and for the most part have a similar incidence and prevalence throughout the globe (see Table 256-1). In contrast, the clinical onset of various rheumatic diseases is often characteristic of certain age groups (e.g., ranging from auto-inflammatory diseases typically presenting in childhood to polymyalgia rheumatica or osteoarthritis presenting in older age groups) and gender (with increased prevalence of autoimmune diseases in women and gout in men). A variety of medications taken chronically can be linked to specific rheumatic syndromes. Positive family histories are not uncommon in patients with autoimmune and other rheumatic disorders.

1. With regard to imaging of gout, the following statement(s) is (are) true:

- A. The presence of periarticular articular erosions and soft tissue nodules are pathognomonic.
- B. Osteopenia is a hallmark of the disease.
- C. Dual-energy computed tomography can be of value to assess disease extent.
- D. It has a characteristic appearance on ultrasound in these patients.
- E. C and D are correct.

Answer: E Dual-energy CT is well suited to assess the distribution of tophaceous deposits in patients with gout because of differences of the absorption characteristics of sodium urate crystals compared

with other types of deposition diseases. On ultrasonography, calcification along the superficial margin of the cartilage is characteristic of gout, giving rise to a double-line sign.

2. A patient presents with radial-sided wrist pain that extends proximally into the forearm. What imaging test(s) would assess possible etiologies?

- A. Radiographs alone should be adequate
- B. MRI
- C. Ultrasonography
- D. B and C are correct
- E. A and B are correct

Answer: D The clinical history suggests DeQuervain's tenosynovitis. Radiographs would allow assessment of the osseous structures but not the adjacent tendons. Although MRI would provide the most complete examination of the radial-sided structures, ultrasonography is well suited to evaluating the soft tissues, including the first dorsal compartment tendons. One also could perform ultrasound-guided therapy at the time of diagnosis.

3. A patient is suspected of having sacroiliitis. What imaging study would be appropriate to initially evaluate the patient?

- A. Radiographs of the SI joints
- B. Computed tomography
- C. Nuclear scintigraphy (bone scan)
- D. MRI
- E. Ultrasonography

Answer: A Dedicated radiographic views of the sacroiliac joints should be the first study ordered to assess for possible erosions and may be sufficient to establish the diagnosis. Computed tomography would provide a more sensitive evaluation for subtle erosions as well as the adjacent soft tissues, particularly with the addition of intravenous contrast. Computed tomography provides an ideal method to perform guided therapy or aspiration. A bone scan would provide a sensitive evaluation of the SI joints but findings would be likewise abnormal for trauma, inflammatory, or degenerative etiologies. A bone scan would allow a global assessment of the axial and appendicular skeleton to determine whether other sites are potentially affected. MRI allows the best assessment of the bone, adjacent marrow space, and soft tissues.

4. A patient has shoulder pain and gives a history of prior dislocation. There is an equivocal abnormality on the humeral head on radiographic evaluation. Which additional study should be considered?

- A. Ultrasonography to rule out a rotator cuff tear
- B. Noncontrast computed tomography
- C. Additional specialized radiographs to evaluate the scapula
- D. Direct MR arthrography
- E. Nuclear scintigraphy

Answer: D Although ultrasonography could evaluate the rotator cuff, it does not provide adequate assessment of the capsular labral complex. Cross-sectional imaging with intra-articular contrast would best accomplish this. MR arthrography would be optimal. Direct arthrography has been the method of choice in assessing the glenoid labrum, surrounding ligaments, and capsule. CT arthrography is of value, particularly in the postoperative shoulder, and provides indirect imaging of internal structures by coating them with contrast material. Noncontrast CT would be very limited in assessing the labroligamentous complex, even in the presence of a joint effusion caused by poor soft tissue contrast.

5. A patient with early rheumatoid arthritis is being considered for placement on a DMARD. All of the imaging studies below could assess the level of disease activity and response to therapy *except*

- A. 18FDG scan.
- B. radiographs of the hands and wrists.
- C. gray-scale ultrasonography with power Doppler.
- D. MRI with gadolinium.
- E. parametric MR imaging of distribution volumes of contrast in the extravascular space.

Answer: B Radiographic findings in rheumatoid arthritis usually occur when there has already been irreversible joint damage. Ideally, therapy would be instituted on a radiographically negative patient. The remaining examinations can provide sensitive evaluation of disease activity before the development of either bone or cartilage erosion.

Ch / 260 INHERITED DISEASES OF CONNECTIVE TISSUE

1. Osteogenesis imperfect syndromes demonstrate

- A. intergenic heterogeneity.
- B. intragenic heterogeneity.
- C. variable expression.
- D. pleiotropy.
- E. all of the above.

Answer: E All four of the choices are correct. Mutations in multiple genes can cause OI (intergenic heterogeneity). With a single locus, many different mutant alleles have been discovered (intragenic heterogeneity). Within a given type of OI, relatives with the same mutation can demonstrate different features of varying severity (variable expression). Multiple organ systems are affected in OI (pleiotropy).

2. Which of the following is not a common feature of Marfan syndrome?

- A. Pulmonary arteriovenous malformation
- B. Aortic root dilatation
- C. Mitral valve prolapse
- D. Pulmonic artery dilatation
- E. Aortic dissection

Answer: A All four of the latter choices are common features. Arteriovenous malformations are common in hereditary hemorrhagic telangiectasia but not in Marfan syndrome.

3. Hypertension is a relatively common feature in which syndrome?

- A. Osteogenesis imperfect
- B. Hurler syndrome
- C. Marfan syndrome
- D. Vascular Ehlers-Danlos syndrome
- E. Pseudoxanthoma elasticum

Answer: E Because of partial occlusion of the renal arteries, elevated blood pressure can occur in PXE. None of the other syndromes has a predisposition to hypertension.

4. Which of the following is not a currently accepted approach to management of Marfan syndrome?

- A. Prophylactic surgery of the aortic root
- B. Exercise restriction
- C. Annual echocardiography
- D. Gene therapy
- E. Chronic β -adrenergic blockade

Answer: D At the present time, no approach to correcting the specific mutation in *FBN1* is feasible. All of the other approaches are thought to be beneficial.

5. If treatment is not offered, which of the following conditions is associated with the best prognosis?

- A. Ehlers-Danlos syndrome, hypermobility type
- B. Osteogenesis imperfect, type II
- C. Marfan syndrome
- D. Hurler syndrome
- E. Ehlers-Danlos syndrome, vascular type

Answer: A The hypermobility form of Ehlers-Danlos syndrome has little to no added mortality. Osteogenesis imperfect type II is usually lethal in infancy. Marfan syndrome has reduced life expectancy because of aortic dissection. Patients with Hurler syndrome rarely survive to their third decade. Patients with the vascular form of Ehlers-Danlos syndrome are at high risk of death from arterial or bowel rupture.

Ch / 261 THE SYSTEMIC AUTOINFLAMMATORY DISEASES

1. Which of the following is not commonly associated with the development of AA amyloidosis?

- A. Hyper-IgD syndrome (HIDS)
- B. Familial Mediterranean fever (FMF)
- C. Tumor necrosis factor receptor–associated periodic syndrome (TRAPS)
- D. Muckle-Wells syndrome

Answer: A All of the listed periodic fever syndromes are commonly associated with the development of AA amyloidosis with the exception of hyper-IgD syndrome, which generally has a benign course.

2. Patients with which monogenic autoinflammatory disease often have a history of flaring after routine immunizations?

- A. FMF
- B. HIDS
- C. TRAPS
- D. FCAS

Answer: B Of these syndromes, only HIDS has a substantiated association of flares with routine immunizations. Psychological stress is often cited as a trigger for flares in FMF and TRAPS, and cold exposure triggers a systemic inflammatory flare and hivelike skin lesions in FCAS.

3. A 30-year-old woman of Armenian and Jewish ancestry presents with a life-long history of unexplained febrile episodes. These attacks are variable in length, with the shortest lasting a few days and the longest lasting over 1 month. The fevers are accompanied by severe abdominal pain or pleuritic chest pain, periorbital edema, arthralgia, and a painful migratory erythematous rash. Corticosteroids ameliorate her symptoms. During pregnancy 7 years ago she was totally free of fevers, but she developed a severe attack in the postpartum period. She is currently not experiencing an

attack, but has an erythrocyte sedimentation rate of 85 (Westergren), C-reactive protein of 100 mg/L, urine protein-to-creatinine ratio of 5.3, and serum creatinine of 2.5. Which of the following is most likely true?

- A. The patient probably has familial Mediterranean fever, and should undergo genetic testing for *MEFV* mutations, have a rectal biopsy to rule out amyloidosis, and commence treatment with intravenous colchicine.
- B. The patient has chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE syndrome), with the T75M mutation in *PSMB8*, encoding a component of the immunoproteasome.
- C. The patient has a mutation at a cysteine residue in the extracellular domain of the p55 TNF receptor and possible amyloidosis. She should undergo a rectal biopsy and should be treated with etanercept or anakinra in an effort to normalize her acute phase reactants.
- D. The patient has a mutation in the *NLRP3* (*CIAS1*) gene, and could be treated with anakinra, rilonacept, or canakinumab for neonatal-onset multisystem inflammatory disease (NOMID).

Answer: C Despite the demographic information that may point toward FMF, the presence of longer disease flares of longer than 7 days, periorbital edema, painful migratory rash, and remission of symptoms with pregnancy are all characteristic of the TNFR1-associated periodic syndrome (TRAPS). Patients with TRAPS and structure-disrupting mutations in TNFR1 have an elevated risk for amyloidosis. TRAPS does not have a predilection for a specific ethnic group or geographic location.

4. A 3-year-old boy of northern European ancestry presents to the autoinflammatory disease clinic for an initial evaluation. Per his mother's report, he began experiencing febrile attacks at the age of 3 months that last 4 to 5 days and occur every 1 to 2 months. Associated symptoms include a nonpruritic macular rash and oral ulcers, and on three occasions he has had genital ulcers. He tends to have flares approximately 2 days after immunizations and after routine viral illnesses. There is no family history of febrile illnesses. He is treated with ibuprofen and acetaminophen and has been given a couple of courses of prednisolone without complete resolution of symptoms. He had been well before his visit, but his mother thinks he is starting to have a flare. On physical examination, he has conjunctival injection, cervical lymphadenopathy but no rashes, oral or genital ulcers, or arthritis. Laboratory studies reveal an ESR of 57 mm/ hour, CRP of 55 mg/L, and IgD level at the top of the normal range. Which of the following is most likely true?

- A. The patient probably has periodic fever with aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA). He should be given either 1 mg/kg of prednisolone at the onset of symptoms or anakinra 2 mg/ kg SC for 1 to 2 days at the onset of symptoms.
- B. The patient has Behçet's disease and should consider colchicine for his oral ulcers. He should undergo HLA typing to assess for the presence of HLA-B51 or other Behçet's-associated MHC findings.
- C. The patient has hyperimmunoglobulinemia D syndrome and should initiate therapy with anakinra at the time of flares or weekly etanercept. He should be tested for mutations in the *MVK* gene.
- D. The patient has cyclic neutropenia and should be tested for mutations in the *ELA-2* gene. He should also have weekly CBC drawn to assess for periodic neutropenia.

Answer: C Despite the oral and genital ulcers that might suggest Behçet's disease, the history of flares after vaccinations or viral illness, the pattern and age of onset, and the ethnic background more strongly suggest that the patient has hyperimmunoglobulinemia D syndrome. IgD levels can be normal in this disease, and a normal IgD should not rule out this diagnosis, which can be confirmed by finding a heterozygous mutation in the mevalonate kinase gene.

5. A 16-year-old high school student is evaluated in the emergency department for 18 hours of abdominal pain, pleurisy, and fever. At that time, he had diffuse rebound tenderness, temperature of 102.5° F (39.2°degrees C), and WBC of 17,000/mm³. He was admitted to general surgery and after 12 hours of persistent symptoms, he was taken to the operating room for exploratory surgery. A normal-appearing appendix was laparoscopically removed. Postoperatively, the fever persisted and he was

noted to have a left pleural effusion. Additional history reveals that he has had similar episodes of febrile illness in the past. On physical examination, he has no rash but has moderate abdominal tenderness with guarding and a left pleural friction rub. Laboratory data reveal an ESR of 80 mm/hour and a negative ANA and RF. While waiting for the results of genetic testing, which of the following medications is *most* appropriate to start at this time?

- A. Indomethacin, 50 mg orally three times daily
- B. Prednisone, 40 mg orally daily
- C. Colchicine, 0.6 mg orally twice daily
- D. Anakinra, 100 mg subcutaneously daily
- E. Acetylsalicylic acid, 1000 mg orally daily

Answer: C The duration of fevers, association with pleural and peritoneal inflammation, and lack of other localizing symptoms are most consistent in this case with familial Mediterranean fever. Colchicine is effective in the prophylaxis of future attacks in FMF. Indomethacin and prednisone can be of some value in terminating attacks but should be reserved for refractory cases. Anakinra can be effective in the treatment of refractory FMF, but there is no need to use this agent in patients who respond to colchicine.

Ch / 263 **BURSITIS, TENDINITIS, AND OTHER PERIARTICULAR DISORDERS AND SPORTS MEDICINE**

1. A 78-year-old woman who has had periodic discomfort in her neck and radiating to both shoulders for several years had a fall, landing on her outstretched right arm. She had pain in the right shoulder and weakness on use. At the urgent care center she was found to have some pain on passive motion and was unable to actively abduct the right shoulder. She had a positive drop arm sign of the right shoulder but not of the left one. All upper extremity deep tendon reflexes were normal. Which of the following is the *most likely* diagnosis?

- A. Rotator cuff tendinitis is the main diagnosis.
- B. X-ray examination of the humerus of the injured side is not indicated in this case because tendon injuries are not visualized on plain x-ray film of the shoulder.
- C. Bicipital tendinitis is the likely diagnosis.
- D. A tear of the rotator cuff best fits as the diagnosis.
- E. Cervical spine disc herniation is the most likely diagnosis based on the history of neck pain and arm weakness.

Answer: D Acute trauma is often the cause of rotator cuff tears, although most tears occur gradually through chronic tendinitis. The positive drop arm sign is typical of a significant rotator cuff tear. Sometimes with trauma, a humeral fracture can occur along with the rotator cuff tear. Pain on abduction and especially on resisted abduction are seen in rotator cuff tendinitis; also, the drop arm sign is typically negative. Bicipital tendinitis usually does not cause shoulder weakness. The clinical picture does not fit a cervical disc herniation, and the reflexes are normal.

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2. A 51-year-old male insurance agent, whose hobby is wood working, complains of right hand pain of approximately 4 months' duration. He had been doing more wood working during that period until the hand pain began to limit this activity. On examination there were no Heberden's nodes of the DIP joints, and the PIP and MCP were not tender or swollen. Moderate-to-severe tenderness on palpation was present over the palm side of the hand at the region of the second and third metacarpal bones. Some swelling was detected at these sites. Crepitus was noted on palpation on flexion of these two digits. Which of the following is the *most likely* diagnosis?

- A. Because rheumatoid arthritis is a likely diagnosis, you should obtain RF, ANA, and hand x-ray films.
- B. Because of his age, he most likely has osteoarthritis of the hand.
- C. He fits the picture of volar flexor tenosynovitis
- D. A C7 radiculopathy would best explain pain in this part of his hand.
- E. Overuse of his hands has caused carpal tunnel syndrome.

Answer: C Volar flexor tenosynovitis is one of the most common musculoskeletal syndromes and is frequently overlooked. It is manifest by pain in the palm of the hand. The volar flexor tendon sheath is tender on palpation and thickened. Triggering or snapping of the digit sometimes occurs, especially when more chronic. Overuse of the hand is the usual cause, but is also seen in association with OA of the hands and diabetes. Stretching of the involved digit and an injection of a small amount of a corticosteroid into the tendon sheath is usually helpful.

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3. A 48-year-old male professional cellist, whose hobby is gardening, has had a 4-month history of right shoulder pain. Pain occurs on various movements of the shoulder, and there is some limitation of movement. Night pain in bed is also reported. On examination, pain limits active abduction to 90 degrees. Less pain is noted on passive abduction, and 180 degrees of abduction is present. The drop arm sign is negative, but pain occurs on active internal rotation of the shoulder. There is no crepitus. Which of the following is the *most likely* diagnosis?

- A. Rotator cuff tendinitis is the most likely diagnosis.
- B. Rotator cuff tear best fits this clinical picture.
- C. Rupture of the biceps tendon is the diagnosis because the drop arm sign is negative.
- D. Adhesive capsulitis (frozen shoulder) is the diagnosis.
- E. OA of the shoulder (glenohumeral joint) is the likely diagnosis, and a plain x-ray film of the shoulder is needed to confirm the diagnosis.

Answer: A The typical physical examination findings of rotator cuff tendinitis are pain on active abduction, less pain on passive abduction, and more pain on resistive abduction. Loss of motion on active movements can occur when more severe. Also, pain may occur on active internal and on external rotation. In addition to the physical examination, ultrasonography and MRI can detect tendinitis, but not plain x-ray examination. In adhesive capsulitis restriction, the range of motion in all directions is usually seen. The full range on abduction and other motions in this case are not typical of a frozen shoulder. OA of the shoulder would not have had a pain history of only 4 months, and it is a much less frequent entity than rotator cuff tendinitis. Crepitus on range of motion is very common in OA of the glenohumeral joint.

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4. A 76-year-old woman with a known history of moderate OA of both knees and a partially torn right medial meniscus experienced pain in her right knee after stooping down to clean something off the floor. The next day she had discomfort and fullness behind her right knee and swelling of her lower leg and ankle. She was able to walk but had a limp. She was seen that day by her primary care physician for evaluation. Which of the following is the *best* course of action?

- A. Begin treatment with heparin or enoxaparin for a deep vein thrombosis.
- B. Give oral prednisone for 5 days as a tapering dose for an acute flare of the OA of her knee.
- C. Obtain a new x-ray film of the knees, with a standing AP and lateral view of the involved leg.
- D. Because of the acute flare of knee symptoms, give colchicines for a possible acute attack of gout.
- E. Obtain a Doppler ultrasound of the right leg for a deep vein thrombosis and an ultrasound image of the right knee to identify a Baker's cyst that has dissected, causing a pseudothrombophlebitis picture.

Answer: E Popliteal cysts, also known as Baker's cysts, are often asymptomatic. However, at times they may enlarge as a result of increasing pressure from a synovial effusion of the knee, flowing through a one-way valve from the knee to the popliteal cyst. The cyst can at times dissect downward, causing swelling of the leg and simulating thrombophlebitis. Thus, the name given to the syndrome is pseudothrombophlebitis. The swelling of the leg may resolve on its own after several days. Often, a corticosteroid injection into the knee joint may help by decreasing the inflammation and synovial effusion of the knee. OA of the knee should not produce swelling of the lower leg, nor should gout. Treatment with anticoagulants should not be given unless the diagnosis of DVT were confirmed.

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5. A 52-year-old moderately obese man complains of pain in his right foot that has been present for approximately 4 months. The pain has become worse recently, and he has had to stop the walks he was taking for exercise. The pain is described to be more in the rear foot and is particularly bad when he first gets out of bed in the morning. He has no history of gout or other arthritis except for some back pain. On examination there is no joint swelling. He does have pes cavus, and tenderness of the plantar surface of the rear foot. His calf muscles are also tight. What is the *most likely* diagnosis and/or the *best* course of evaluation and treatment?

- A. Order an MRI of the foot or technetium bone scan for possible stress fracture.
- B. Inject the calcaneus with a steroid, because that is the best initial treatment for heel pain.
- C. Make a tentative diagnosis of plantar fasciitis and treat with analgesics, stretching of calf and plantar fascia, and use of a heel cushion as the initial treatment.
- D. Obtain uric acid level and start treatment with colchicine.
- E. Obtain orthopedic consultation for possible Achilles tendon tear.

Answer: C The complaint of morning foot pain, which is called "first step pain," is typical of plantar fasciitis. Tenderness often elicited on pressure exerted on the plantar surface of the calcaneus. Trauma to the foot from prolonged walking, tight calf muscles, high arched foot with tight plantar fascia, and obesity are factors related to acquiring plantar fasciitis. A steroid injection of the calcaneal area is often helpful, but is not the first line of treatment. With Achilles tendinitis/tear the pain is in the posterior heel and not the plantar surface. A stress fracture is more likely to occur in the metatarsal area and only very rarely occur in the calcaneus.

Biundo, JJ: Regional Rheumatic Pain Syndromes, Primer on the Rheumatic Diseases, Thirteenth Edit. 2006

Ch / 264 RHEUMATOID ARTHRITIS

1. A 32-year-old woman presents with 3 weeks of symmetrical swelling and stiffness in her PIPs and MCPs. The most helpful laboratory test result in establishing a diagnosis of RA in this patient would be:

- A. ESR of 65 mm/hour.
- B. RF of 120 IU (normal <40).
- C. Anti-CCP of 87 (normal <20).
- D. Positive ANA.

Answer: C The presence of anti-CCP antibodies in a patient with an inflammatory arthritis is 99% specific for the diagnosis of RA even when it is only of short duration as in this patient with only 3 weeks of disease. This is critically important because it allows very early institution of DMARD therapy. The presence of a positive ANA, an elevated RF, or elevated ESR would not be particularly helpful—all are nonspecific.

2. A 40-year-old attorney is diagnosed with RF- and CCP-positive rheumatoid arthritis. His mortality is increased, and he is most likely to die from which of the following?

- A. Lymphoma
- B. Pulmonary fibrosis from RA
- C. Infections related to RA and its therapies
- D. Coronary artery disease

Answer: D Heart disease is by far the biggest killer of patients with RA. Rheumatologists should do everything possible to get disease activity under control, and PCPs should do everything possible to control other risk factors, including ideal management of BP and cholesterol. RA patients have at least a two-fold increased risk for lymphoma, have increased risk for infections (particularly when treated with steroids or biologic agents), and can get pulmonary fibrosis, but these all have a small impact compared to that of heart disease.

3. A 28-year-old accountant with RA is considering another pregnancy. Reasons for concerns for conception and the health of her fetus during the first trimester include which of the following?

- A. She is currently on 5 mg of prednisone.
- B. She is currently taking sulfasalazine.
- C. She has a history of treatment with leflunomide.
- D. She is taking Naprosyn 500 mg.

Answer: C Leflunomide is a significant teratogen and has a half-life that is extremely prolonged. Any potential mother who has ever taken it needs blood levels drawn before conception. Leflunomide can be rapidly eliminated from the body by treatment with cholestyramine. Prednisone is considered safe in pregnancy; significant data suggest that sulfasalazine is well tolerated by both mother and child and NSAIDs are safe until the last trimester.

4. A 52-year-old woman with RA treated with methotrexate and adalimumab presents to the ER with fevers, cough, and increasing shortness of breath. A chest x-ray film shows diffuse patchy infiltrates. You would:

- A. Admit, stop her adalimumab, and give her broad-spectrum antibiotics.
- B. Admit, stop both her adalimumab and methotrexate, and aggressively pursue workup for infectious and inflammatory etiologies.
- C. Treat her for community-acquired pneumonia.
- D. Admit, stop adalimumab, and aggressively pursue workup for infectious etiology.

Answer: B All TNF inhibitors have a black box warning for fatal opportunistic infections. Tuberculosis, histoplasmosis, coccidioidomycosis, pneumocystis, legionellosis, and others have all been reported. The key to patient survival is aggressive diagnosis so appropriate treatment can be started rapidly. Methotrexate can be associated with unusual infections rarely, but the biggest concern here is that the patient may have methotrexate pneumonitis. This can be fatal if the methotrexate is not stopped. It usually presents with low-grade fevers, nonproductive cough, increasing dyspnea, and patchy infiltrates on chest x-ray films. Treatment of methotrexate pneumonitis after stopping methotrexate is usually supportive, but occasionally high-dose steroids may be indicated.

5. A 55-year-old carpenter is newly diagnosed with RA. His medical history includes type II diabetes for 15 years. CBC shows low-grade anemia with normal red cell indices, Hgb A1c is 7, creatinine is 2.1, and urinalysis shows 3+ proteinuria. Laboratory studies are otherwise unremarkable. Appropriate initial DMARD therapy would be:

- A. Cyclosporine.
- B. Hydroxychloroquine.
- C. Methotrexate.
- D. Sulfasalazine.

Answer: B Although methotrexate at the doses used to treat RA rarely affects the kidney, well-functioning kidneys are important for the clearance of methotrexate. Methotrexate, if used, should be used with extreme caution and close monitoring in this situation. Cyclosporine, although effective in some cases of RA, also has renal toxicity and is not a good choice. Hydroxychloroquine is the best choice here—in addition to being effective against RA, it has been shown to lower blood sugar, particularly in type II diabetes. Additionally, patients with RA who are on hydroxychloroquine have a 60% reduction in their risk for incident diabetes. Finally, sulfasalazine would be a possible choice but not as good as hydroxychloroquine.

Ch / 265 **THE SPONDYLOARTHROPATHIES**

1. A 28-year-old man presents with a 2-year history of low back pain and intermittent arthritis in the lower extremity. Physical examination demonstrates bilateral Achilles tendonitis and tenderness to direct pressure over the sacroiliac joints. Which of the following would **not** support the diagnosis of spondyloarthritis (SpA)?

- A. Presence of HLA-B27
- B. History of anterior uveitis
- C. Positive rheumatoid factor
- D. Elevated CRP
- E. History of inflammatory bowel disease

Answer: C The history and the other optional features would be entirely consistent with a diagnosis of SpA. HLA-B27 is strongly associated with SpA in general, and its strongest association is with ankylosing spondylitis (AS). Anterior uveitis occurs in approximately 30% of AS cases, and is itself associated with HLA-B27 even when AS is not present. Positive rheumatoid factor is characteristic of rheumatoid arthritis but not of SpA, so it would not be expected to be positive in such patients. Elevated C-reactive protein (CRP) is a nonspecific marker of inflammation and would be commonly seen in patients with active SpA. Inflammatory bowel disease occurs in approximately 10% of AS cases, and its presence strongly suggests that concurrent musculoskeletal inflammation that the underlying arthritis is part of the SpA spectrum.

2. A 32-year-old man presents with pain and swelling of one ankle and one knee. The history reveals that he had just returned from a trip to South America and developed diarrhea that was now subsiding. He denied any eye inflammation or skin lesions. Physical examination confirmed tenderness and swelling of an ankle and a knee. The next appropriate diagnostic test would be which of the following?

- A. Aspiration of the knee swelling and culture of the synovial fluid
- B. Initiate a course of broad-spectrum antibiotics.
- C. X-rays of the lumbar and cervical spine
- D. Check a blood test for the presence of antinuclear antibodies.
- E. Initiate an empirical trial of methotrexate.

Answer: A A patient with new-onset swelling in the joints, particularly when one or two joints are affected, should always raise the possibility of septic arthritis. When there has been a recent infection elsewhere in the body, it is possible the inciting infection could spread by a hematogenous route to seed the joint. Although the history is suggestive of reactive arthritis (ReA), it is important to rule out septic arthritis with certainty before entertaining that diagnosis. Culture of synovial fluid is the definitive test to rule out septic arthritis.

Empirical use of broad-spectrum antibiotics rarely has a place in the management of new-onset arthritis. The first step is to make a diagnosis. X-rays of the spine are important in the evaluation of inflammatory back pain, but in this case there is only peripheral joint involvement. If the course of the

arthritis becomes chronic or back pain develops over time, x-rays at that point would be appropriate. Antinuclear antibodies in the serum are the hallmark of many autoimmune rheumatic diseases—in particular, lupus. But with the clinical presentation in this case, there are no features to implicate lupus or related conditions, and it would not be appropriate to search for antinuclear antibodies. The immediate priority is to rule out septic arthritis. It would be inappropriate to institute methotrexate before that is resolved.

3. A 30-year-old man presents with worsening back pain. The history reveals that this has been present for the past 3 years and is increasing in severity. It is characterized by early-morning stiffness, nocturnal pain, and modest improvement with exercise. He initially noted an improvement with an NSAID, but subsequently that effect was lost, and he has tried two other NSAIDs without effect. Physical examination reveals limitation in forward flexion of the lumbar spine. An AP x-ray of the pelvis reveals bilateral erosive changes in the sacroiliac joints. A lateral x-ray of the lumbar spine reveals squaring of several vertebral bodies. The next step in pharmacologic treatment of this condition is which of the following?

- A. Methotrexate
- B. Leflunomide
- C. Sulfasalazine
- D. TNF inhibitor biologic agents
- E. Azathioprine

Answer: D The patient meets the diagnostic criteria for ankylosing spondylitis (AS). He has long-standing back pain that has features of inflammatory back pain and has limitation in spinal mobility. The presence of bilateral erosive sacroiliitis provides imaging support for the diagnosis of AS. He has had an adequate trial of NSAIDs, and his back pain has not responded adequately to these agents. The classical DMARDs used in rheumatoid arthritis—methotrexate, leflunomide, sulfasalazine, and azathioprine—have proved ineffective in controlling the spinal inflammation seen in AS. On the other hand, the TNF inhibitors (infliximab, etanercept, adalimumab, golimumab) have established efficacy in controlling the signs and symptoms of AS.

4. A 35-year-old woman is under your care for ankylosing spondylitis (AS). She is HLA-B27 positive and has no extra-articular features accompanying her back pain. Her symptoms have been controlled with NSAIDs in combination with physiotherapy and exercises. She has an 8-year-old son, and she is inquiring about his current and future health prospects. Which of the following would be advisable in this circumstance?

- A. The son should be checked for HLA-B27 status.
- B. The mother should be advised that the likelihood of her son developing AS is less than 10%.
- C. The son should be advised to avoid sports and physical activities.
- D. Preventive low-dose NSAIDs should be instituted for the son.
- E. The son should be advised to avoid foreign travel in order to avoid food-borne pathogens.

Answer: B There is a 50% chance that any particular child of a B27-positive patient will be B27 positive, but there is only a 20% chance of a B27-positive individual with a positive family history developing AS. So the likelihood of a child developing AS when he has a B27-positive parent with AS is maximally 10%. It would not be advisable to test an asymptomatic child for HLA-B27, because it has low predictive value (as discussed earlier) and could introduce chronic anxiety about future disease, which is unwarranted. There is no reason to limit the sports and recreation of the child. Maintaining general fitness and muscle strength and posture is sound advice even if there is a greater chance of later arthritis than in the general population. There is no evidence that sports-related injuries trigger AS. There is no evidence that NSAIDs prevent the subsequent development of SpA in individuals who are genetically predisposed to SpA. Chronic NSAID therapy carries its own risks and would not be justified in an asymptomatic individual. There is a theoretical concern that being B27 positive could increase the risk of reactive arthritis after a food-borne pathogen illness. This might lead to advising a patient

with **prior** diagnosis of ReA to minimize exposure to food-borne pathogens, but it would be inappropriate to restrict travel for anyone who has never had an episode of ReA.

5. A 19-year-old female patient has developed a painful swollen knee over the course of 7 days. There is no history of trauma and no associated skin lesions or ocular complaints. The patient relates a history that she has just returned from a trip abroad with the family and had a transient diarrheal episode while traveling. Further questioning reveals that she has had two prior episodes of diarrhea in the past year, each associated with crampy abdominal pain, but on each occasion the diarrhea was self-limited and she did not seek medical attention. Which of the following would **not** be an appropriate next step in the management of this patient?

- A. Referral to a gastroenterologist for ileocolonoscopy
- B. Culture of a stool sample
- C. Aspiration of the knee and culture of synovial fluid
- D. Check hemoglobin and ESR.
- E. Institute a 2-week course of ciprofloxacin.

Answer: E The patient has developed arthritis in the setting of a recurrent diarrheal course. The key differential is between reactive arthritis (ReA) and enteropathic arthritis (EA) as part of inflammatory bowel disease (IBD). In either case, it would be inappropriate to institute an empirical course of antibiotics before a diagnosis is made. In neither postdysenteric ReA nor in IBD-associated arthritis is there evidence that antibiotics alter the course of the arthritis. It would be appropriate in this case to determine whether the recurrent diarrhea could be a manifestation of Crohn's disease or ulcerative colitis, and ileocolonoscopy would be indicated to address that question. Recurrent diarrhea might reflect a infectious agent such as *Salmonella*. Stool cultures would be an appropriate test to address that. Culture of synovial fluid is the definitive test to rule out septic arthritis. Both *Salmonella* and *Yersinia* can cause a septic arthritis, so it is appropriate to exclude an infection in the joint before proceeding to other management decisions. Anemia of chronic disease might raise the suspicion that a chronic process, such as IBD, has been present for some time. Elevation in CRP or ESR is appropriate in the work-up of this patient, although this would not differentiate ReA from IBD-related arthritis. These acute phase reactants can serve as useful surrogate markers to monitor response to treatment.

Ch / 266 **SYSTEMIC LUPUS ERYTHEMATOSUS**

1. Data from genome-wide association studies identify gene variants encoding the following proteins as associated with a diagnosis of systemic lupus erythematosus (SLE):

- A. Major histocompatibility complex class I
- B. Interferon regulatory factor 5 (IRF5)
- C. Interferon- γ
- D. Interleukin-17
- E. Adiponectin

Answer: B Polymorphisms in IRF5 are associated with SLE. IRF5 is a transcription factor that is activated following cell triggering through endosomal toll-like receptors and induces transcription of type I interferon and other proinflammatory mediators. Although MHC class II alleles are associated with a diagnosis of SLE, associations with class I alleles have not been reported. Interferon- γ and interleukin-17 are T-cell products that may be implicated in lupus pathogenesis, but significant genetic polymorphisms in their genes have not been associated with SLE. Adiponectin is a product of adipocytes and has not been described as having a role in lupus susceptibility.

2. Environmental factors can trigger initiation or exacerbation of SLE. One mechanism by which drug-induced lupus can be triggered is through:

- A. Induction of T regulatory cells
- B. Damage to renal podocytes
- C. DNA demethylation
- D. Increased proteinuria
- E. Hemolysis

Answer: C Procainamide is an antihypertensive agent that has been associated with induction of lupus. This drug impacts gene expression and cell function through demethylation of DNA, resulting in self-reactive T cells. T regulatory cells contribute to protection from autoimmune disease rather than induction of autoimmune disease. Damage to podocytes might be one mechanism of renal damage but has not been associated with drug-induced lupus. Increased proteinuria and hemolysis are clinical manifestations of lupus but do not represent mechanisms that account for drug induced lupus.

3. Clinical manifestations of lupus can include:

- A. Seizures
- B. Renal failure
- C. Myocardial infarction
- D. Pericarditis
- E. All of the above

Answer: E The clinical manifestations of lupus are protean and can effect any organ system. It should be noted that premature atherosclerotic cardiovascular disease is frequent among lupus patients and can contribute to increased mortality.

4. Autoantibodies specific for the following antigen are specific for SLE:

- A. Ro
- B. Centromere
- C. RNP
- D. Scl70
- E. Sm

Answer: E Autoantibodies associated with a diagnosis of SLE include those targeting protein components of ribonucleoprotein particles, such as Ro, which is also associated with Sjögren's syndrome and rheumatoid arthritis. Anti-RNP antibodies can be seen in patients with SLE or mixed connective tissue disease. Anti-centromere and anti-Scl70 antibodies are associated with systemic sclerosis. Anti-Smith (Sm) antibodies are nearly exclusive to patients with SLE.

5. Which therapeutic agent is appropriate for both induction and maintenance therapy for class III or IV lupus nephritis?

- A. Intravenous pulse glucocorticoid therapy
- B. Azathioprine
- C. Cyclophosphamide
- D. Mycophenolate mofetil
- E. Rituximab

Answer: D Induction therapy for lupus nephritis is often conducted with cyclophosphamide, along with IV pulse glucocorticoid therapy. However, recent data indicate that mycophenolate mofetil (MMF) can be as effective as cyclophosphamide. In addition, MMF has shown efficacy as a maintenance therapy. IV pulse glucocorticoid therapy and cyclophosphamide are appropriate for induction therapy but should not be used as a chronic maintenance therapy for lupus nephritis. Azathioprine is appropriate as a maintenance therapy but is inferior to other options as induction therapy. Rituximab has not shown efficacy in randomized controlled clinical trials for lupus nephritis, but nonetheless is sometimes used in that clinical setting if other therapies are not successful.

Ch / 267 **SYSTEMIC SCLEROSIS (SCLERODERMA)**

1. Which of the following does not contribute to the pathogenesis of systemic sclerosis (SSc)?

- A. Vascular wall remodeling
- B. Tissue fibrosis
- C. Vasculitis
- D. T cells
- E. Hypoxia

Answer: C Vasculitis does not typically occur in SSc. Vascular remodeling leading to hypoxia, inflammation, and fibrosis are the hallmarks of the disease.

2. Which is a characteristic autoantibody seen in SSc patients?

- A. Anticentromere
- B. Anti-CCP
- C. Antihistone
- D. Antiphospholipid
- E. Anti-Smith

Answer: A Anticentromere is a hallmark SSc-associated autoantibody, whereas the other autoantibodies are seen in rheumatoid arthritis (B), lupus (C, E), and the antiphospholipid syndrome (D).

3. Which is a major factor in SSc morbidity?

- A. Glomerulonephritis
- B. Episcleritis
- C. Amyloidosis
- D. Pulmonary hypertension
- E. Bowel infarction

Answer: D Pulmonary hypertension develops in up to 15% of SSc patients and is a major cause of morbidity and mortality. The other clinical features are uncommon in SSc and indicate other autoimmune or rheumatic diseases.

4. In patients with SSc-associated lung disease, lung biopsy may show:

- A. Honeycombing
- B. Interstitial fibrosis
- C. Plasma cell accumulation
- D. Intimal proliferation in the small vessels
- E. All of the above

Answer: E All of the listed pathologic features can be noted in lung biopsies from patients with SSc-associated interstitial lung disease.

5. Which of the following drugs may contribute to scleroderma renal crisis?

- A. NSAIDs
- B. Glucocorticoids
- C. Mycophenolate
- D. Rituximab
- E. Penicillamine

Answer: B The use of glucocorticoids has been shown to increase the risk of new-onset scleroderma renal crisis in patients with SSc.

1. A 59-year-old woman is referred to your office because of dry mouth, grittiness of eyes, and a rash on both legs. Physical exam discloses unilateral parotid enlargement and a purpuric rash of the lower extremities. Past medical history is unremarkable to date. Among the following diagnostic tests, which one is the most useful to establish the diagnosis of Sjögren syndrome?

- A. Complement levels
- B. Cryoglobulins
- C. Serum protein electrophoresis
- D. Salivary flow
- E. Anti-Ro/SSA antibodies

Answer: E Anti-Ro/SSA positivity is one of the two required 2002 European/American classification criteria for Sjögren syndrome (SS) and one out of the three 2012 preliminary ACR/SICCA 2012 criteria. Low complement levels, especially C4, and cryoglobulinemia have been designated as adverse prognostic factors for lymphoma development and mortality among SS patients. However, they are not included in the classification criteria. Hypergammaglobulinemia or monoclonal gammopathy are likewise not included in the classification criteria of SS. Salivary flow rate of less than 1.5 mL/15 minutes is an objective criterion of oral dryness, included in the 2002 European/American classification SS criteria but not in the 2012 preliminary ACR/SICCA criteria. It is not as specific as anti-Ro/SSA antibodies.

2. A 55-year-old woman presents with mild pain affecting her hands, as well as ocular and mouth dryness for 10 years. Her examination reveals positive ocular staining for both eyes, revealing keratoconjunctivitis sicca, positive anti-Ro/SSA antibodies, and negative HCV and HIV serology. Additional testing included complete blood count, revealing lymphopenia with normal hemoglobin levels and platelet counts. Mixed monoclonal cryoglobulinemia and low C4 levels were also detected. Which of the following statements is true?

- A. The patient fulfills both the the 2002 American/European Consensus Group (AECG) criteria and 2012 preliminary ACR/SICCA criteria for primary SS (pSS).
- B. The patient fulfills only the 2002 AECG criteria for pSS.
- C. A minor salivary gland biopsy is mandatory to classify the patient as having SS according to 2002 AECG group criteria for pSS.
- D. A minor salivary gland biopsy is mandatory to classify the patient as having SS according to 2012 preliminary ACR/SICCA criteria for pSS.
- E. The patient suffers from sicca asthenia polyalgia syndrome.

Answer: A Two out of three 2012 preliminary ACR/SICCA criteria are fulfilled, as well as four out of six 2002 AECG criteria. Since anti-Ro/SSA antibodies are present, no histopathologic confirmation is required for the classification of pSS according to 2002 AECG criteria in the presence of subjective and objective symptoms and signs of salivary and lacrimal gland involvement. Sicca asthenia polyalgia syndrome is a diagnosis of exclusion and refers to the presence of fibromyalgia-like features in association with sicca symptomatology.

3. Which of the following is the best option for improving the patient's ocular dryness?

- A. Methotrexate
- B. Pilocarpine
- C. Hydroxychloroquine
- D. Ocular cyclosporine drops
- E. Infliximab

Answer: D Ocular cyclosporine drops have proved useful in the treatment of dry eye. The efficacy of methotrexate on ocular dryness has never been demonstrated. Ocular dryness is less frequently

improved than salivary dryness with secretagogues (i.e., pilocarpine). The efficacy of hydroxychloroquine on dryness has not been demonstrated. No efficacy of infliximab has been demonstrated in pSS.

4. Which of the following features is **not** considered an adverse predictor for lymphoma development in Sjögren syndrome?

- A. Presence of splenomegaly
- B. Presence of purpura
- C. Salivary flow rate less than 1 mL/15 minutes
- D. Presence of persistent parotid gland enlargement
- E. Presence of CD4 lymphopenia

Answer: C All the other items are predictive factors of lymphoma. An association has not been reported between salivary flow rate and risk of lymphoma development.

5. A 55-year-old woman is referred to your department for polysynovitis and palpable purpura. She fulfills the AECG 2002 criteria for Sjögren syndrome. Which of the following treatments would you recommend to treat these systemic manifestations?

- A. Infliximab
- B. Intravenous immunoglobulin
- C. Pilocarpine
- D. Rituximab
- E. Cyclophosphamide

Answer: D Three randomized controlled trials (RCTs) and one registry study suggested possible efficacy of rituximab in pSS, at least in some systemic manifestations. Two RCTs did not demonstrate any efficacy of tumor necrosis factor blockers (i.e., infliximab) in pSS. IVIG has been proposed in open studies in the treatment of SS-associated neuropathies without vasculitis, but never has demonstrated any efficacy in other systemic manifestations. The secretagogue pilocarpine has no effect on systemic manifestations. The systemic manifestation presented by the patient is not severe enough to propose cyclophosphamide.

Ch / 269 INFLAMMATORY MYOPATHIES

1. A 65-year-old man developed slowly progressive difficulty arising from a chair and experienced buckling of the knees while walking, resulting in several falls. Muscle biopsy showed endomysial inflammation and rimmed vacuoles. The correct diagnosis is:

- A. Polymyositis
- B. Dermatomyositis
- C. Inclusion body myositis
- D. Immune-mediated necrotizing myopathy
- E. Overlap syndrome

Answer: C Inclusion body myositis (IBM). IBM is a later-onset, slowly progressive disease presenting with prominent quadriceps or finger flexion weakness. In this case, the knee buckling indicates quadriceps weakness. Endomysial inflammation can be seen in either polymyositis or IBM, but rimmed vacuoles confirm IBM as the correct diagnosis.

2. A 35-year-old woman developed proximal weakness and a purplish papular rash over the dorsum of the hands. A skin biopsy might be expected to show what feature and lead to which diagnosis:

- A. Lymphocytoclastic vasculitis AND polymyositis
- B. Interface dermatitis AND dermatomyositis
- C. Granulomas AND granulomatous myositis
- D. Necrotic cells AND necrotizing myopathy
- E. Necrotic cells AND dermatomyositis

Answer: B This patient has Gottron's papules (see Fig. 296-2A), virtually pathognomonic for dermatomyositis. Skin biopsy in dermatomyositis shows an interface dermatitis, with pathology of the basal layer of keratinocytes lying at the border (interface) between the epidermis and the dermis.

3. A 60-year-old man with proximal weakness and mildly elevated serum creatine kinase (CK) is diagnosed with polymyositis and treated with high-dose prednisone 80 mg/day for several months, before slow taper of prednisone to 30 mg/day by month 6. His serum CK improves, but no improvement in strength is present and he appears mildly weaker. Which statement is most likely true?

- A. He has refractory polymyositis and needs more aggressive therapy.
- B. He has developed steroid myopathy in addition to his polymyositis.
- C. The diagnosis of polymyositis should be reconsidered, and he could undergo a second muscle biopsy or blood diagnostic testing for anti-cN1A autoantibodies as the next step.
- D. The diagnosis of polymyositis should be reconsidered; he may have inclusion body myositis or a limb-girdle muscular dystrophy.
- E. C and D

Answer: E Patients with IBM in particular, and sometimes limb-girdle muscular dystrophy, are often misdiagnosed as having polymyositis. Serum CK, modestly elevated in IBM, may lower with prednisone treatment, but patients rarely have improved strength.

4. Which syndrome can be paraneoplastic and should prompt thorough investigation for an underlying malignancy?

- A. Dermatomyositis
- B. Polymyositis
- C. Inclusion body myositis
- D. Granulomatous myositis
- E. All of the above

Answer: A Dermatomyositis. A new diagnosis of dermatomyositis should prompt a thorough investigation for an underlying malignancy, with reported rates estimated at 15 to 23%.¹² The types of malignancy found in patients with dermatomyositis generally reflect those found in age-, sex-, and population-matched persons without dermatomyositis. Therefore, breast, lung, and colorectal cancer are the three most common cancers from Western country cohorts, while nasopharyngeal carcinoma is the most common dermatomyositis-associated cancer in Asian studies. This finding further supports the role of dermatomyositis as a paraneoplastic process that can occur with virtually any kind of cancer. (Ungprasert P, Bethina NK, Jones CH. Malignancy and idiopathic inflammatory myopathies. *N Am J Med Sci*. 2013;5:569-572.)

5. Normal serum CK in a patient with proximal muscle weakness excludes the diagnosis of:

- A. Dermatomyositis
- B. Inclusion body myositis
- C. Muscular dystrophy
- D. Granulomatous myositis
- E. None of the above

Answer: E None of the above. Serum CK is a helpful indicator of muscle disease when elevated, but normal CK does not exclude muscle disease. In particular, patients with very active dermatomyositis frequently have normal serum CK.

Ch / 270 **THE SYSTEMIC VASCULITIDES**

1. Immunosuppressive therapy is known to be futile for which disease associated with vascular inflammation?

- A. Buerger disease (thromboangiitis obliterans)
- B. Granulomatosis with polyangiitis (formerly Wegener granulomatosis)
- C. IgA vasculitis (Henoch-Schönlein purpura)
- D. Giant cell arteritis
- E. Mixed cryoglobulinemia

Answer: A The only effective intervention known for Buerger disease is smoking cessation. Neither immunosuppression nor anticoagulation is of any demonstrable benefit in relieving the severe digital ischemia associated with this disease.

2. Which form of systemic vasculitis is most likely to present with an orbital pseudotumor?

- A. Takayasu arteritis
- B. Granulomatosis with polyangiitis (formerly Wegener granulomatosis)
- C. Microscopic polyangiitis
- D. Polyarteritis nodosa
- E. Behçet syndrome

Answer: B Two common ocular manifestations of granulomatosis with polyangiitis are scleritis and orbital pseudotumor. The latter can lead to proptosis and vision loss if blood circulation to the eye is compromised by the retrobulbar mass.

3. A 24-year-old man from Lebanon presents with multiple aphthous ulcers, bilateral ocular erythema, tender erythematous nodules over his anterior legs, and a deep venous thrombosis. An ophthalmologic examination reveals severe bilateral uveitis affecting both the anterior and posterior compartments of the eye. In addition to anticoagulation and the institution of glucocorticoid therapy, what is the most appropriate approach to treating his disease at this time?

- A. Intravenous cyclophosphamide
- B. Azathioprine
- C. Intravenous immunoglobulin
- D. Tumor necrosis factor inhibition
- E. B-cell depletion

Answer: D Tumor necrosis factor inhibition is highly effective in Behçet disease and is employed in the presence of severe disease manifestations such as posterior uveitis or central nervous system (CNS) disease.

4. A 32-year-old woman presents with the rapid onset of the worst headache of her life 1 day after giving birth to a healthy baby boy. The delivery followed an uneventful pregnancy. The patient has no history of migraine headaches, and her past medical history is unremarkable. The patient's blood pressure is 140/90 mm Hg, and although her neurologic examination is nonfocal, the severity of the headache prompts a computed tomographic (CT) scan of the brain. This is negative for an intracranial

bleed, and the headache resolves after approximately 24 hours, during which time it was profoundly disabling.

Approximately 18 hours later, the headache returns, again rising to a crescendo within several minutes of onset. A repeat head CT is negative and a lumbar puncture is also performed, revealing a normal opening pressure, 1 white blood cell/mL (100% lymphocytes), and a cerebrospinal fluid protein of 40 mg/dL (normal 30 to 50 mg/dL). The headache improves following round-the-clock narcotic treatment but then worsens again on the third postpartum day. A magnetic resonance imaging study is negative for hemorrhage, cerebral infarctions, and masses, but a four-vessel cerebral angiogram shows alternating areas of vascular narrowing and dilatation (beading) in multiple vascular distributions.

What is the most appropriate intervention for this patient now?

- A. Tighter blood pressure control, with transfer to the intensive care unit for sodium nitroprusside therapy
- B. Addition of a baby aspirin to her anticoagulation with low-molecular-weight heparin
- C. Pulse methylprednisolone (1000 mg/day for 3 days) followed by prednisone 60 mg/day and cyclophosphamide 100 mg/day
- D. Nifedipine 30 mg three times daily
- E. Proceed to brain biopsy

Answer: D Nifedipine. This patient has a history that is classic for reversible cerebral vasoconstriction syndrome (RCVS), an entity that mimics CNS vasculitis but is not an inflammatory condition. The features suggesting RCVS in this patient are the presence of a “thunderclap” headache, the nonfocal neurological examination, the normal cross-sectional imaging and lumbar puncture, and the diffuse beading on angiography. This beading represents vasospasm, which is the essential pathophysiology of RCVS. Calcium-channel blockers are often used in therapy, but prolonged courses of immunosuppression are not indicated. Brain biopsy can be diagnostic in primary angiitis of the CNS, but would not be indicated in a patient like this who has typical clinical and radiographic features of RCVS.

5. A 4-year-old boy presents with 3 days of a febrile illness with temperatures to nearly 105° Fahrenheit. Physical examination reveal an erythematous “strawberry” tongue, swollen lips, and a pink macular rash on the trunk. There is also tender cervical and axillary lymphadenopathy and diffuse swelling of the distal upper and lower extremities. Which treatment is indicated immediately now to prevent the occurrence of coronary aneurysms?

- A. Intravenous immunoglobulin
- B. High-dose aspirin therapy
- C. Pulse methylprednisolone
- D. Plasma exchange
- E. Anticoagulation with heparin

Answer: A This child has Kawasaki disease, and the most feared complication of this disorder is formation of coronary aneurysms, which can lead to myocardial infarction. If administered in a timely manner, intravenous immunoglobulin prevents the occurrence of such aneurysms.

1. A 74-year-old gentleman presents with a 7-week history of increasing generalized shoulder and hip pain, morning stiffness, low-grade fevers, and a dry cough. He was found to be anemic with a hemoglobin of 9.7 and had a thrombocytosis with a platelet count of 642 and an elevated sedimentation rate of 114. A search for infection and neoplasia has been unrevealing, including a bone marrow biopsy, which did not suggest a myeloproliferative neoplasm. He denies headaches, visual symptoms, or jaw claudication. The patient has reluctance regarding any further interventional procedures. Which of the following would be the best option to establish his diagnosis?

- A. A computed tomographic (CT) angiogram with imaging of the aortic arch and its major branches
- B. A conventional angiogram
- C. Duplex ultrasound of his temporal arteries and axillae.
- D. A positron emission tomography (PET) scan
- E. Bilateral temporal artery biopsies

Answer: E The patient likely has giant cell arteritis. Although PET scanning, duplex ultrasound of temporal arteries, and CT angiography may be helpful in some patients, a temporal artery biopsy remains the gold standard and is the most specific if the biopsy can be established. Duplex sonography has yet to be proved reliably accurate. PET scanning and angiography, although potentially helpful, can provide in false-positive results in patients with severe atherosclerosis and false-negative results in patient without clear evidence of large vessel disease. Polymyalgia rheumatica (PMR) may be a possibility here (and this patient indeed has PMR), but the presence of dry cough and degree of inflammatory response makes concurrent giant cell arteritis (GCA) a pressing concern

2. A 77-year-old woman with a history of diabetes, osteoporosis, and modest alcohol use presents with 3 weeks of headaches and feeling systemically unwell and then loss of vision in her left eye 2 days ago. She is found to be anemic with a markedly elevated sedimentation rate, and a temporal artery biopsy confirms the diagnosis of GCA. She is started on 60 mg of daily prednisone. Which of the following would be an appropriate additional intervention at this point?

- A. Add Infliximab 5 mg/kg monthly as a steroid-sparing intervention.
- B. Add methotrexate 10 mg weekly with the hope of titrating that to 15 mg weekly to afford a steroid-sparing benefit.
- C. Change her corticosteroid regimen to 120 mg on alternate days and plan an alternate day taper from there.
- D. Add low-dose aspirin daily to her regimen.
- E. Add tocilizumab 8 mg/kg monthly as a steroid-sparing intervention.

Answer: D Patients with GCA often struggle with comorbidities that raise concerns regarding prolonged exposure to corticosteroids. There is at this time, however, no proven steroid-sparing intervention that can decrease the risk for cranial ischemic complications or even that has been demonstrated to reduce corticosteroid-related adverse events. Low-dose aspirin has been shown in two retrospective studies to be likely protective against cranial ischemic complications, so if there is no contraindication, that would be an appropriate intervention. Methotrexate has been shown in one trial in one individual meta-analysis to have a corticosteroid benefit in terms of cumulative steroid dose and also reduced risk for flares, but in the largest multicenter study addressing its efficacy, it was not shown to be superior to placebo. Moreover, in this patient with comorbidities including diabetes and alcohol use, methotrexate could be morbid, so this would not seem an appropriate intervention at this point. Infliximab has been shown in a randomized, double-blinded, placebo-controlled trial not to be helpful in the treatment of GCA and can increase risk for infection in this patient already on high doses of corticosteroids with underlying diabetes. Alternate-day corticosteroid therapy has been shown to increase the risk for later flare and is not generally employed in GCA, particularly earlier in the course of treatment. Tocilizumab, an interleukin-6 inhibitor, is an agent of great interest in temporal arteritis,

but it has not yet been shown to have a corticosteroid-sparing or disease-modifying benefit in this disorder; however, trials are presently in progress addressing this issue.

3. A 72-year-old man presents with a 2-month history of morning stiffness, mild synovitis in his knees, puffiness in his hands in the early morning hours, and severe shoulder and thigh girdle myalgias. He is mildly anemic with hemoglobin of 11.6 and has a markedly elevated sedimentation rate at 82. He is seronegative for rheumatoid factor, citric citrullinated peptide (CCP), and antineutrophil cytoplasmic antibodies. He has no evidence of peripheral joint erosions on plain radiographs. Which of the following would be the most appropriate therapeutic intervention at this point?

- A. Begin naproxen 500 mg twice daily.
- B. Begin methotrexate 10 mg weekly with the hope of bringing that dose up to 15 mg weekly in the next few weeks.
- C. Begin methylprednisolone 12 mg daily.
- D. Begin hydroxychloroquine 200 mg twice daily.
- E. Begin methylprednisolone 12 mg daily along with methotrexate 10 mg weekly with a plan to taper the corticosteroids to off over the next 4 weeks.

Answer: C The patient described has PMR but presents with some peripheral synovitis, which can be seen in up to 10 to 15% of patients with PMR. The patient clinically is unlikely to have rheumatoid arthritis in the absence of seropositivity for rheumatoid factor and CCP, has typical shoulder and thigh girdle myalgias and morning stiffness, and does not have evidence of erosive disease radiographically. An initial trial of methylprednisolone 12 mg daily would have both therapeutic and likely diagnostic value because if his response is spectacular, that would strongly argue for PMR and continuing that approach to therapy. Although methotrexate and hydroxychloroquine have been agents of interest in polymyalgia rheumatica, their use has not been well established in double-blinded, placebo-controlled trials. One study suggesting a benefit to methotrexate in PMR did not demonstrate a benefit in terms of reducing numbers of corticosteroid-related adverse events, and at longer term follow-up, the initial benefits seen by the addition of methotrexate did not seem to persist. Naproxen would be unlikely to afford adequate relief to this patient and, given his comorbidities, would likely be as problematic if not more problematic than a trial of corticosteroids.

4. An 80-year-old gentleman with a prior history of giant cell arteritis successfully treated 7 years earlier presents with searing chest pain. His past medical history is otherwise only notable for borderline hypertension. He was successfully treated with a 1-year course of steroids but has been free of corticosteroids for 3 years. He has been feeling systemically well until recently. He had not seen a physician in 2 years. Which of the following explanations for his chest pain is of primary concern?

- A. Dissecting thoracic aneurysm
- B. Acute pericarditis
- C. A myocardial infarction related to his increased risk for atherosclerosis given his prior history of GCA
- D. Costochondritis related to a flare of PMR
- E. Rib fracture

Answer: A Patients with a prior history of GCA are at increased risk for thoracic aortic aneurysms, even several years after completing therapy without evidence of residual active disease. The searing quality of his pain and his prior history of treated GCA make this a concern that should not be missed. The quality of his pain did not sound suggestive of a myocardial infarction, and patients with GCA have not been demonstrated to be at increased risk for atherosclerotic heart disease, although the possibility of that association has been of interest. Patients with GCA are not particularly at a higher risk for pericarditis. Although PMR can arise even years after successfully treated GCA (or even years after successfully treated PMR), the quality of his pain does not sound suggestive thereof, and costochondritis would not typically be a feature of PMR. The quality of the pain described did not sound suggestive of a rib fracture, but moreover that would be a diagnosis that could be overlooked at least initially without putting the patient at increased risk for a serious cardiovascular compromise.

5. A 72-year-old woman had presented with an 8-week history of progressively increasing morning stiffness, shoulder and thigh girdle myalgias and arthralgias, and fatigue. An extensive search for underlying infection and age-appropriate screening for underlying neoplasm were unrevealing. A serum immunofixation did not reveal a monoclonal gammopathy. She was found to be anemic with a hemoglobin of 10.7 and had a sedimentation rate of 108. She denied any headaches, scalp sensitivity, jaw claudication, or visual symptoms. She admitted to low-grade fevers but not greater than 100° F. PMR was suspected, and she was treated with methylprednisolone 12 mg daily in divided doses. Three days later, she called to report no significant improvement in her symptoms. It was suggested that her dose be raised to 16 mg daily in divided doses. She comes in for evaluation still complaining of similar myalgias and arthralgias, and her sedimentation rate remains elevated at 62, although her hemoglobin improved slightly to 10.9. Which of the following would be an appropriate next intervention?

- A. Add methotrexate as a disease-controlling/steroid-sparing intervention.
- B. Add infliximab to help achieve disease control.
- C. Refer her for a bone marrow biopsy to exclude underlying myeloproliferative or lymphoproliferative disease.
- D. Add hydroxychloroquine 400 mg daily.
- E. Refer her for a temporal artery biopsy and raise the methylprednisolone to 32 mg daily.

Answer: E This patient presented with fairly typical PMR symptoms but in addition had low-grade fevers, which can be seen but are not as common as they are in GCA. Moreover, she was somewhat anemic. Her lack of response to 12 mg and then even 16 mg of daily methylprednisolone makes PMR unlikely unless in the context of a more substantial inflammatory disease such as GCA. GCA is found in approximately 10% of patients with “pure” PMR, and conversely, up to 50% of patients with GCA can present with PMR-like symptoms.

Ch / 272 INFECTIONS OF BURSAE, JOINTS, AND BONES

1. A 55-year-old man with a history of diabetes has had a chronic ulcer over the fifth metatarsal head with some swelling and pain for the past 5 weeks, following what he thought was a minor trauma. On examination, bone can be palpated with a probe. Which of the following is most likely?

- A. The white blood cell count is elevated.
- B. There is a high probability that the patient has osteomyelitis.
- C. The best imaging test to define the cause of the pain is a gallium scan.
- D. The best imaging test to define the cause if the pain is plain bone radiography.
- E. The most likely cause of a possible infection is *Fusobacterium* species infection.

Answer: B The ability to palpate bone by probing the overlying ulcer is highly suggestive of osteomyelitis. Patients with contiguous chronic osteomyelitis often have normal white blood cell counts and are often afebrile. Magnetic resonance imaging is the best (most sensitive) radiographic technique for demonstrating bone damage consistent with osteomyelitis. Overall, *Staphylococcus aureus* is the most common cause of osteomyelitis, but in patients with diabetic foot bone osteomyelitis, the infection is often polymicrobial (see Table 280-1).

2. A 32-year-old carpet layer presents with a 3-day history of swelling of the right knee. The father and grandfather of the patient developed gout as young men. The patient had a single episode of right toe pain and swelling 3 months earlier, which he attributed to “kicking carpet into place.” He has a temperature of 38.7° C. Examination of the right knee reveals erythema and swelling, most prominently over the anterior aspect of the knee, but extending around the soft tissues about the knee. With some pain, he is able to completely extend the knee, although he cannot comfortably flex it beyond 80 degrees. The prepatellar bursa is aspirated. The white blood cell count is 750. Which of the following is correct?

- A. The knee joint should also be aspirated and joint fluid sent for culture and sensitivity.
- B. The low white blood cell count in the bursal fluid makes it unlikely that the bursa is infected.
- C. Gram stain examination of the bursal fluid will almost always guide therapy.
- D. Urate crystals will not be found on microscopic examination.
- E. A magnetic resonance imaging (MRI) study must be obtained to rule out osteomyelitis.

Answer: B This patient has prepatellar bursitis, which is usually due to direct tissue invasion, in this case likely related to local tissue invasion in the setting of chronic soft tissue trauma associated with kneeling and local friction of the overlying skin. Bursal fluid is often unobtainable, but if it can be obtained, the white blood cell count in the aspirated bursal fluid in the setting of septic bursitis is generally low compared with the WBC count in septic arthritis, on average 13,500 cells in the bursal fluid. Gram stain is positive in only about 15% of cases of septic bursitis. Urate crystals may be seen in cases of gouty bursitis, which can occur concomitantly, but should not distract from the possibility of septic bursitis. MRI is the most sensitive imaging technique to evaluate osteomyelitis in routine clinical practice, but there is nothing in this case to cause suspicion of bone infection.

3. Which of the following is true regarding septic arthritis?

- A. Most cases are due to direct inoculation of the joint from trauma or surgical procedures such as arthrocentesis.
- B. Gonococcal arthritis is the most common form of septic arthritis in persons aged 20 to 40 years.
- C. Hematogenous spread of tuberculosis is the most common cause of septic arthritis in persons from developing countries immigrating to Western countries of Europe, North American, and Australia.
- D. Blood cultures are frequently positive in septic arthritis.
- E. Intravenous vancomycin and daptomycin are the mainstays of treatment for most cases of septic arthritis in the immunocompetent host in the current era of multiple antibiotic resistance.

Answer: D About 75% of cases of septic arthritis are due to hematogenous spread, including surgical instrumentation. Although gonococcal arthritis must be considered in sexually active patients, 50 to 70% of cases of septic arthritis are due to *Staphylococcus aureus*. Although almost all cases of septic tuberculous arthritis in Western countries occur in immigrants from developing countries, most cases of septic arthritis in these patients are still due to nontuberculous bacteria. Blood cultures should always be obtained in persons with septic arthritis. They are positive in up to 50% of cases, even in cases when the joint aspirate fails to microscopically reveal the causative organism. Although multiple antimicrobial resistance is a serious problem, most cases of uncomplicated septic arthritis in the otherwise healthy host can be managed with an oral antistaphylococcal penicillin or first-generation cephalosporin.

4. A 76-year-old man with a history of osteoarthritis arthritis and total joint replacement of the right hip at the age of 70 years presents with a 2-day history of right groin pain and temperature to 39.5° C 3 days after finishing a 1-week course of levofloxacin for an infected ingrown toenail. He is allergic to penicillins. Empirical antibiotic therapy with vancomycin for presumed staphylococcal prosthetic joint infection is started. The synovial fluid aspirate from the prosthetic right hip is negative, but blood cultures reveal *S. aureus*, methicillin resistant. His prosthesis was not loose on plain-film examination. Which of the following is true regarding prosthetic infections in this patient?

- A. A biofilm with polymicrobial bacterial colony-forming units is frequently present, complicating eradication of the organism. Explantation of the prosthesis is always needed in such cases.
- B. The most appropriate antimicrobial therapy in this case would be linezolid 600 mg PO/IV every 12 hours.
- C. Risk factors for prosthetic joint infection *include* wound healing complications, prior superficial surgical site infection, prior infection of the joint, osteoarthritis, and diabetes mellitus.
- D. Because of the occurrence of prosthetic infection in this patient following hematogenous spread of the causative bacterium, the best course of action would be explantation of the prosthesis at this time, followed by 4 to 6 weeks of antibiotic therapy without reimplantation.

E. The best course of action would be to attempt salvage of the prosthesis with débridement and retention and 2 to 6 weeks of effective intravenous antibiotic therapy and rifampin based on the recently published Infectious Diseases Society of America Prosthetic Joint Infection guidelines (Osmon DR, Berbari EF, Berendt AR, et al. Infectious Diseases Society of America. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;56:e1-e25), followed by chronic suppressive therapy with oral antimicrobial agents.

Answer: E Biofilms are often found in explanted infected prosthesis and complicate successful antimicrobial therapy. These biofilms are polymicrobial in about 20% of cases. Risk factors for prosthesis infection include rheumatoid arthritis, but not osteoarthritis. In most cases of acute infection, management efforts are directed toward treating the infection and attempting to salvage the prosthesis. When resection arthroplasty is needed, 4 to 6 weeks of pathogen-directed intravenous therapy is typical before an attempt at reimplantation several weeks later.

5. A 68-year-old woman with a history of chronic atrial fibrillation and diabetic neuropathy presents with a 5-day history of subacute swelling and pain in the left ankle. She reports that she “turned” her ankle while gardening about a week ago. Her temperature is 36.7° C. Inspection of the ankle reveals moderate erythema and swelling. The skin is intact; sensation to touch is diminished in both feet. The remaining history and physical examination are unrevealing, including examination of the oral cavity. The sedimentation rate is 42 mm/hour; white blood cell count is 9800 mm³, and INR is 3.2. Which of the following strategies should be pursued in management of this patient?

- A. Blood cultures and empirical therapy with vancomycin 15 mg/kg every 12 hours or daptomycin 6 mg/kg/IV every 24 hours for presumed methicillin-resistant *Staphylococcus aureus* (MRSA). Avoid arthrocentesis because of the elevated INR and risk for worsening joint damage due to hemarthrosis and the danger of hematogenous spread of the infection.
- B. Blood cultures, empirical therapy with vancomycin 15 mg/kg every 12 hours or daptomycin 6 mg/kg/IV every 24 hours for presumed MRSA, and arthrocentesis for examination of synovial fluid Gram stain and culture
- C. Blood cultures, empirical therapy with aqueous crystalline penicillin G 20 × 10⁶ U every 24 hours IV either continuously or in six equally divided daily doses or ampicillin sodium 12 g every 24 hours IV either continuously or in six equally divided daily doses. Avoid arthrocentesis because of the elevated INR and risk for worsening joint damage due to hemarthrosis and the danger of hematogenous spread of the infection.
- D. Blood cultures, empirical therapy with aqueous crystalline penicillin G 20 × 10⁶ U every 24 hours IV either continuously or in six equally divided daily doses or ampicillin sodium 12 g every 24 hours IV either continuously or in six equally divided daily doses, and arthrocentesis for examination of synovial fluid Gram stain and culture

Answer: B A source of infection was not identified in this patient, who has risk factors for septic arthritis of diabetes mellitus and diabetic neuropathy. Because even in these cases the most common cause of septic arthritis is gram-positive cocci, particularly *Staphylococcus aureus*, initial treatment directed at this organism is appropriate. It is not unreasonable to initiate therapy with an MRSA-appropriate regimen. Arthrocentesis should always be performed if there is suspicion of septic arthritis; bleeding complications, even in patients on anticoagulation, are rare, and the information potentially gained generally justifies the risk for the procedure.

1. The prevalence of hyperuricemia in the United States has been rising dramatically over the past three decades because of all of the following *except* which one?

- A. Increased longevity of the population
- B. Increased use of low-dose aspirin and thiazide diuretics
- C. Greater consumption of low-fat dairy products
- D. Greater consumption of high-fructose corn syrup
- E. Increased prevalence of the metabolic syndrome

Answer: C The aging population, the increasing prevalence of the metabolic syndrome, and increased consumption of medications and diets that increase blood uric acid levels by either inhibiting its excretion (low-dose aspirin and thiazide diuretics) or increasing its production (high-fructose corn syrup) are all factors leading to the increased prevalence of hyperuricemia and gout in the United States. Increased consumption of low-fat dairy products does not cause hyperuricemia.

2. Which one of the following is true regarding renal clearance of uric acid?

- A. Comparable in gouty and nongouty subjects
- B. Reduced in gouty subjects by 70%
- C. Proportional to the serum urate levels in both gouty and nongouty subjects
- D. Controlled by components of the “transportosome” in the distal nephron
- E. Reduced by the angiotensin II receptor blocker losartan

Answer: C Gouty subjects have reduced renal clearance of uric acid, and their excretion of uric acid is reduced by only 30% (not 70%). The renal tubular transporters (collectively called the *transportosome*) that are responsible for determining how much of the filtered uric acid is actually excreted are located in the proximal convoluted tubules, not the distal nephron. Renal clearance of uric acid is not reduced by losartan.

3. Factors that may provoke flares of gout include all of the following *except* which one?

- A. Initiation of allopurinol
- B. Overindulgence in shellfish
- C. Starvation
- D. Initiation of colchicine
- E. Surgery

Answer: D Initiation of colchicine can actually block flares of gout. In contrast, allopurinol or any other drug or factor that alters blood uric acid levels (either up or down) can provoke an acute gouty attack.

4. According to the American College of Rheumatology (ACR) 2012 treatment guidelines for urate-lowering therapy, which one of the following is true?

- A. Prophylactic anti-inflammatory therapy should be initiated before starting allopurinol or febuxostat.
- B. Patients with chronic kidney disease should not be treated with more than 300 mg of allopurinol daily.
- C. Serum urate levels should be reduced to less than 5 mg/dL in all patients with gout.
- D. The initial starting dose of allopurinol is 300 mg daily in most patients.
- E. Probenecid is first-line therapy for patients with chronic kidney disease stage 3 or 4.

Answer: A Prophylactic anti-inflammatory drugs should be initiated before starting allopurinol or febuxostat because any acute change in uric acid levels (including acute changes that actually reduce the levels, as these drugs would do, as well as increase the levels) can precipitate an acute gout attack. The ACR guidelines recommend starting allopurinol at doses of 100 mg daily in those without kidney disease or 50 mg daily in those who do have advanced chronic kidney disease, followed by dose escalations of 100 mg or 50 mg in these situations, respectively. ACR guidelines recommend a

target serum uric acid of less than 6 mg/dL, except in those with advanced gout, whose levels should be lowered to less than 5 mg/dL. The uricosuric agent, probenecid, is recommended only as addition to a first-line xanthine oxidase inhibitor if target urate levels cannot be attained with maximum doses of the latter.

5. The laboratory investigation for underlying metabolic causes of calcium pyrophosphate dehydrate (CPPD) deposition disease would include all of the following, *except* which one?

- A. Serum ferritin
- B. Serum calcium and phosphate
- C. Serum alkaline phosphatase
- D. Serum magnesium
- E. Serum lead

Answer: E Metabolic diseases that predispose to CPPD crystal deposition disease include hemochromatosis, hyperparathyroidism, hypomagnesemia states, and hypophosphatasia. *Saturnine gout* is the term used to describe gout (not CPPD crystal deposition disease) caused by chronic lead exposure (e.g., by occupational exposure or drinking “moonshine” whiskey).

6. The basic calcium crystal arthropathy referred to as *Milwaukee shoulder* is characterized by which one of the following?

- A. Bilateral involvement in men
- B. Destruction of the glenohumeral joint
- C. Markedly inflammatory synovial fluid
- D. Birefringent crystals in the synovial fluid
- E. Slow progression

Answer: B The form of BCP arthropathy known as Milwaukee shoulder has a predilection for elderly women, is usually unilateral but can involve the knees, and has non-inflammatory synovial fluid (WBC <1,000 per cubic mm) that is usually bloody in appearance. Despite non-inflammatory fluid the condition can be rapidly destructive.

Ch / 274 **FIBROMYALGIA, CHRONIC FATIGUE SYNDROME, AND MYOFASCIAL PAIN**

1. A 45-year-old woman presents with a 2-year history of pain and swelling in her hands and aching muscles. Which of the following is the most likely diagnosis?

- A. Rheumatoid arthritis
- B. Fibromyalgia
- C. Systemic lupus erythematosus
- D. Hand osteoarthritis with concomitant fibromyalgia
- E. Dercum disease

Answer: D Hand osteoarthritis is especially common in women, as is fibromyalgia. Although fibromyalgia patients often complain of joint swelling, this is never observed clinically. Thus, the most likely diagnosis is a combination of fibromyalgia and hand osteoarthritis. Early rheumatoid arthritis can have this presentation, but after 2 years, other joints, especially the feet, would be symptomatic. Dercum disease is a rare disorder characterized by multiple painful lipomas.

2. A 47-year-old woman presents with a 2-year history of pain and stiffness in her right shoulder without swelling. She has a full range of motion in the shoulder but has pain when stretching forward. She reports that she feels a “bump” in the upper shoulder muscles. Which of the following is the most likely diagnosis?

- A. Polyarteritis nodosa
- B. Fibromyalgia
- C. A focal myofascial trigger point
- D. Fibrosarcoma of the trapezius muscle
- E. Polymyositis

Answer: C This is the typical presentation of a myofascial trigger point in the shoulder girdle muscles. The pain associated with myofascial trigger points is aggravated by full range of motion. Most patients with myofascial pain problems are aware of a “tight knot” in the involved muscles. Polymyositis is a generalized autoimmune disorder of muscle that usually presents as proximal muscle weakness; pain is seldom a major symptom.

3. Chronic fatigue syndrome (CFS) has a population prevalence of which of the following?

- A. 2%
- B. 8 to 10%
- C. Less than 1%
- D. 0.001% to 0.003%
- E. 4 to 8%

Answer: C CFS is less prevalent than fibromyalgia, which has a prevalence of about 2% in the general population. However, most population studies in CFS report a prevalence of 0.006 to 3.0%. This is in contradistinction to a complaint of fatigue, which is one of the most common symptoms seen by family doctors.

4. The clinical features of myofascial trigger points often include all *except* which of the following?

- A. Pain referred distally when the trigger point is palpated for 1 second
- B. Pain referred distally when the trigger point is palpated for between 5 and 10 seconds
- C. Restricted movement in involved muscle
- D. A tight “knot” in the involved muscle
- E. Pseudo-weakness of the involved muscle

Answer: A A critical clinical feature of a myofascial trigger point is distally referred pain after about 5 or more seconds of steady pressure over the tight knot. A common mistake in evaluating myofascial trigger points is to just prod them without exerting prolonged pressure. The patient needs to be asked to report pain or discomfort occurring in an area outside the tight knot during palpation; this referred pain is usually distal to the trigger point. This feature is even more marked when a trigger point is needled.

1. A 30-year-old man complains of a several-months history of joint pain involving his hands, wrists, knees, and ankles. He reports chronic swelling but no acute attacks of synovitis. He has been taking up to eight acetaminophen tablets a day to control the pain. He denies rashes, nodules, pleuritic chest pain, or dyspnea. He reports no family history of arthritis. His father died of liver cancer. Physical examination is remarkable for synovial thickening over his metacarpophalangeal joints (MCPs), wrists, and ankles. He has small effusions in both knees. His skin examination shows darkened skin but no nodules. Radiographs show joint space narrowing, sclerosis, and osteophytes of his MCPs and radiocarpal joints. Which one of the following tests is most likely to support this patient's diagnosis?

- A. Iron studies
- B. Anti-cyclic citrullinated peptide (CCP) antibodies
- C. Liver-associated enzymes
- D. Urine homogentisic acid
- E. Morning serum cortisol

Answer: A This patient has hemochromatotic arthropathy, which would be supported by abnormal iron studies (elevated iron, % transferrin saturation, and ferritin). Up to 33% of patients with hemochromatosis present with arthritis as their initial manifestation. Osteoarthritic involvement of MCPs, wrists, and ankles, coupled with dark skin demonstrating a grayish hue, are characteristic. The osteoarthritic changes on radiographs excludes rheumatoid arthritis, so an anti-CCP antibody would not be helpful. Although liver-associated enzymes may be elevated, other stigmata of liver disease are absent early in the course of hemochromatosis. However, the early diagnosis and treatment of this patient and affected family members will help prevent cirrhosis and possible liver cancer, which developed in his father. A urinary homogentisic acid level will be normal. Ochronosis can cause dark skin, but the arthritis presents in the lumbar spine with osteoarthritis and calcified vertebral discs. Addison's disease (primary adrenal insufficiency) likewise causes hyperpigmentation, but it is not typically associated with rheumatic manifestations.

2. A 32-year-old woman complains of painful lower extremity nodules and bilateral ankle arthritis over the past 5 days. She denies fever, sore throat, cough, chest or abdominal pain, or dysuria. Past history is significant for two urinary tract infections and one episode of pelvic inflammatory disease. She has a family history of a mother who died with ovarian cancer. Her only medication is birth control pills. Physical examination shows normal vital signs. She has bilateral swelling and tenderness of her ankles. Several 2- to 3-cm erythematous, tender nodules are on the extensor surfaces of both lower legs. The remainder of the examination is unremarkable. Which one of the following tests should be ordered now to support this patient's clinical diagnosis?

- A. Nodule biopsy
- B. Ankle joint synovial fluid analysis
- C. Cervical culture for *Neisseria gonorrhoeae*
- D. Chest radiograph

Answer: D This patient has a presentation consistent with acute sarcoidosis manifested by erythema nodosum and bilateral ankle arthritis (Sweiss NJ, Patterson K, Sawaged R, et al. Rheumatologic manifestations of sarcoidosis. *Semin Respir Crit Care Med.* 2010;31:463-473). A person with bilateral ankle arthritis should always be investigated for possible sarcoidosis. Despite negative pulmonary symptoms, a chest radiograph will show bilateral hilar adenopathy supporting the clinical diagnosis of Löfgren's syndrome. A nodule biopsy would show a septal panniculitis consistent with erythema nodosum, which could be from a cause other than sarcoidosis such as birth control pills. Synovial fluid aspiration is usually unsuccessful and always nondiagnostic in a patient with an acute sarcoidosis presentation. A cervical culture in an asymptomatic patient is unlikely to be useful, and disseminated gonococcemia typically presents with fever, arthritis, and a vesiculopustular rash, but not nodules.

3. A 72-year-old woman complains of a 3-week history of bilateral progressive hand pain unresponsive to naproxen, prednisone, and oxycodone. She denies fever, rash, or Raynaud's phenomenon. She has had a 10-pound weight loss and lower abdominal pain that she attributes to constipation and lack of appetite owing to taking narcotics. Physical examination shows normal vital signs. She has bilateral metacarpophalangeal and proximal interphalangeal joint swelling and tenderness. She has diffuse swelling, erythema, and tenderness that follow the track of the flexor tendons of the digits. Straightening the fingers causes intense pain. Shoulder examination shows decreased internal rotation bilaterally. The remainder of the joint, heart, and lung examinations were normal. Tests obtained in the emergency room last week showed normal hand radiographs except for soft tissue swelling and chondrocalcinosis of the wrists. Rheumatoid factor and antinuclear antibody were negative. Which one of the following tests would be most important to obtain next?

- A. Magnetic resonance imaging (MRI) of the hands
- B. Anti-CCP antibody
- C. Bimanual pelvic examination
- D. Synovial fluid aspiration and crystal examination

Answer: C This patient is presenting with the palmar fasciitis and polyarthritides syndrome (PFPAS). This presentation is highly associated with ovarian cancer when it occurs in an elderly woman (Shah A, Jack A, Liu H, Hopkins RS. Neoplastic/paraneoplastic dermatitis, fasciitis, and panniculitis. *Rheum Dis Clin North Am.* 2011;37:573-592). Therefore, a bimanual pelvic examination would be the most important test to obtain. MRI of the hands will show palmar fasciitis, which was diagnosed on the clinical examination. Although rheumatoid arthritis can have an acute onset, the lack of response to nonsteroidal anti-inflammatory drugs (NSAIDs) and prednisone makes this diagnosis unlikely. In addition, the rheumatoid factor was negative, so an anti-CCP antibody is unlikely to be positive. Chondrocalcinosis is a common incidental radiographic finding in elderly patients. The multijoint presentation and lack of response to prednisone make acute pseudogout unlikely, and therefore putting the patient through a difficult aspiration of a finger joint looking for crystals is not indicated.

4. A 52-year-old man is admitted to the hospital for joint pain, diarrhea, and weight loss. He reports a 3-year history of palindromic, inflammatory polyarthritides that tends to affect large joints, including the knees, ankles, and wrists. He also has increased lower back pain that is worse at the end of the day. Previous evaluation showed a negative rheumatoid factor, negative antinuclear antibody, and normal hand and wrist radiographs. He states the arthritis lasts several weeks before resolving. NSAIDs, hydroxychloroquine, and methotrexate have been ineffective in reducing the frequency of attacks that occur every few months. Over the past 6 months, he has noted diarrhea and a 20-pound weight loss. He has had mild abdominal discomfort and a decreased appetite. Evaluation showed a normal colonoscopy 4 months ago. An abdominal computed tomography scan showed hepatomegaly and several enlarged periaortic lymph nodes. A 24-hour stool collection revealed steatorrhea. An antitransglutaminase antibody was negative. Physical examination shows a thin male with normal vital signs except a pulse of 100 beats per minute. He has mild hepatomegaly. He has a few enlarged axillary lymph nodes. His right wrist and left knee are swollen. Synovial fluid aspiration from his knee yesterday showed a cell count of 22,100/mm³ with 80% neutrophils. Gram stain and crystal examinations were negative. Laboratory evaluation included the following:

Complete blood count: hematocrit 33%, white blood cell count 7800/mm³, platelets normal

Chemistries: normal

Albumin: 2.7 g/dL

Aspartate transaminase: 51 U/L (normal, 0 to 40)

Urinalysis: normal

Erythrocyte sedimentation rate: 48 mm/hour

Which one of the following tests is most likely to confirm your clinical diagnosis?

- A. Hepatitis C serologies
- B. Esophagogastroduodenoscopy with small bowel biopsy
- C. Anti-*Saccharomyces cerevisiae* antibody
- D. HLA-B27 and sacroiliac joint radiograph
- E. Blood culture

Answer: B This patient has Whipple's disease, which would be diagnosed by a small bowel biopsy (Puechal X. Whipple's disease. *Ann Rheum Dis.* 2013;72:797-803). Patients with Whipple's disease frequently have an intermittent inflammatory arthritis that precedes other manifestations of Whipple's disease by a few years. The patient's more recent weight loss, diarrhea with steatorrhea, hepatomegaly, and lymphadenopathy are other manifestations of Whipple's disease. The small bowel biopsy showing periodic acid-Schiff-positive macrophages and immunohistochemical staining with antisera specific for *Tropheryma whipplei* will confirm the diagnosis. A lymph node or synovial biopsy would show similar diagnostic findings. The recent normal colonoscopy rules out inflammatory bowel disease, so an anti-*Saccharomyces cerevisiae* antibody will not be helpful. Despite an enlarged liver and mild transaminitis, which are also seen in Whipple's disease, hepatitis C would not explain his steatorrhea. The patient's back pain is mechanical because it is worse at the end of the day. Therefore, an HLA-B27 test and sacroiliac joint radiographs will not confirm his diagnosis, nor will these tests explain his diarrhea. Although the patient has an inflammatory synovial fluid, septic arthritis would not follow this clinical course.

5. You are asked to consult on a 64-year-old man hospitalized for aortitis. He was emergently admitted 3 days ago with chest pain from a 6-cm descending thoracic aortic aneurysm and dissection. Pathologic examination of the surgically removed diseased aorta revealed a nongranulomatous aortitis with fibrosis. His past history includes diet-controlled diabetes mellitus and hypertension controlled with lisinopril. One year ago, he had an orbital pseudotumor successfully treated with 3 months of prednisone. He denies fever, headaches, or visual problems. Physical examination was limited because of his recent surgery. Temporal artery pulses were normal. He had atelectatic crackles in both bases. He has 1+ pedal edema. No abdominal bruits or masses. Preoperative laboratories include the following:

Complete blood count: hematocrit 35%, white blood cell count 10,400/mm³, platelets 280,000

Chemistries: normal

Rapid plasma reagin: negative

Aorta histology showed lymphoplasmacytic infiltrate without granulomas or giant cells. Adventitial phlebitis and fibrosis were present. Stains for spirochetes and fungal elements were negative. Which one of the following is most likely to help confirm this patient's diagnosis?

- A. Genetic testing for transforming growth factor- β (TGF- β) receptor mutations
- B. Antineutrophil cytoplasmic antibody
- C. Immunohistochemical staining of tissue for immunoglobulin G4 (IgG4)-positive plasma cells
- D. Temporal artery biopsy

Answer: C This patient has IgG4-related disease (Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med.* 2012;366:539-551). The nongranulomatous, lymphoplasmacytic infiltrate in the aorta is consistent with this. The past history of an orbital pseudotumor is also compatible with this condition. Serum IgG4 level is typically elevated. Immunohistochemical studies would show that the aortic infiltrate was primarily IgG4-producing plasma cells. Genetic testing for TGF- β receptor mutations would not be helpful because this is not the histology seen in patients with Loeys-Dietz syndrome. Antineutrophil cytoplasmic antibody-related vasculitis does not cause aortitis. A temporal artery biopsy would offer no further information not already shown by the aortic histology.

1. A 47-year-old man presents with groin pain of 2 years' duration. The pain is worse with weight-bearing activity, such as standing or walking. On physical examination, the hip demonstrates evidence of limited flexion and internal rotation. He has tried nonsurgical measures, such as oral nonsteroidal anti-inflammatory drugs (NSAIDs), physical therapy, and rest; none has provided any lasting relief. Radiographs demonstrate complete loss of the cartilage space in the hip joint. His bone structure and quality appear to be good. The patient feels extremely debilitated at this point because of his inability to perform activities of daily living (ADLs). In addition to ADLs, the patient would like to have the ability to run, in the future. Which of the following is the most appropriate recommendation?

- A. Hip arthroscopy
- B. Hip resurfacing
- C. Total hip replacement
- D. Fusion of the hip
- E. Bracing of the hip

Answer: B Hip resurfacing is appropriate in this category of patient: a male patient, younger than 65 years. Hip arthroscopy is not likely to alleviate the symptoms in this patient because of full-thickness cartilage loss. Total hip replacement is an option, but the preservation of bone is desirable in younger patients, and impact sports are not advisable with a total hip replacement. Fusion of the hip has essentially become a historical operation: few surgeons perform this anymore because of the superior function of a hip replacement. Bracing of the hip would not be expected to help in situations of complete cartilage loss.

2. A 67-year-old woman presents with knee pain and an increasing deformity over the past 2 years. She notices that her knees are becoming "more bowlegged." With any prolonged weight-bearing activity, she experiences diffuse pain within the knee joint. In addition, the knee swells up on occasion, causing difficulty bending. She has only tried oral supplements such as glucosamine and chondroitin sulfate sporadically for pain relief. Physical examination reveals medial joint line tenderness and a small joint effusion. Her radiographs demonstrate moderate to severe joint space narrowing. The patient desires to return to walking activities and improve motion in her knee. What is the most appropriate recommendation for this patient?

- A. Immediate total knee replacement surgery
- B. Knee arthroscopy
- C. Knee fusion
- D. Partial knee replacement
- E. A trial of nonsurgical measures, such as weight loss, physical therapy, and bracing

Answer: E Given the patient's moderate joint space narrowing and lack of prior nonsurgical interventions, a trial of weight loss, physical therapy, and bracing is worthwhile. Knee arthritis can respond well to this treatment regimen, reducing the stresses on the knee joint and helping the patient delay total knee replacement surgery.

3. Inflammatory arthritis can be distinguished from osteoarthritis by which of the following?

- A. Mechanical overload
- B. Sclerosis
- C. Symmetrical joint space narrowing
- D. Cystic changes
- E. Osteophyte formation

Answer: C The hallmark of inflammatory arthritis is the presence of symmetrical joint space narrowing, a feature best appreciated radiographically. All the other characteristics are those of degenerative disease processes.

4. The advantages of the use of regional (epidural) anesthesia in lower extremity orthopedic surgery include which of the following?
- A. Reduction in blood loss
 - B. Reduction in postoperative thromboembolic complications
 - C. Reduction in postoperative pulmonary complications
 - D. Facilitation of postoperative pain control
 - E. All of the above

Answer: E Regional anesthesia is a popular and commonly employed anesthesiology technique for patients undergoing lower extremity orthopedic procedures for a variety of reasons. Each of the potential advantages listed has been demonstrated with this form of anesthesia in this setting.

5. A 52-year-old obese man undergoes bilateral total hip replacement for severely symptomatic osteoarthritis of the hip. During the surgical procedure, after cementing of the first hip, the anesthesiologist notes a rise in the patient's pulmonary artery pressures that persists through the completion of the surgery. In the recovery room, the patient develops progressive hypoxemia and may require mechanical ventilation. Fat embolism is suspected. What additional sign of this condition is *least* likely to be helpful securing this diagnosis?
- A. Bilateral pulmonary infiltrates
 - B. Mental confusion
 - C. Retinal hemorrhage
 - D. Petechial skin eruption
 - E. Signs of right heart strain

Answer: D All of the above phenomena have been described as important features of classic fat embolism syndrome. Nonetheless, in the postoperative arthroplasty setting, the classic petechial skin eruption is virtually never seen.

Ch / 278 **THE HUMAN MICROBIOME**

1. Which of the following statements is correct regarding the human microbiome?
- A. The human microbiome is a DNA-based analysis of the composition of the indigenous microbial communities throughout an individual's gastrointestinal tract (formerly called normal flora).
 - B. In a healthy individual, the phylogenetic composition of the microbiome remains mostly constant from one anatomic site to another, but the core metabolic functions of these microbial communities vary greatly across anatomic sites.
 - C. Changes in microbiota composition occur during the entire life cycle of an individual, with the most dramatic changes developing after early childhood (after 3 years of age).
 - D. There is strong evidence for an inherited basis of the microbiota, particularly supporting maternal inheritance.
 - E. Metabolic and physical signaling occurs among the microbes but not between the microbes and their host, creating dynamic equilibrium relationships within the microbiome independent of its host.

Answer: D The congruent phylogenies of mammals and their microbiota provide strong evidence for the heritability of the microbiota. In humans, increasing evidence supports a maternal inheritance. Choice A is incorrect because the human microbiome involves much more than the gastrointestinal tract. Indeed, the presence of major clustering patterns at various body sites provides new ways to classify individuals and their potential for disease risks (see Fig. 278-1). Choice B is incorrect because the reverse is true: it is the phylogenetic composition of the microbiome that varies greatly from one anatomic site to another, whereas the core metabolic functions remain remarkably constant and conserved across anatomic sites (see Fig. 278-2). The most dramatic changes in the microbiome occur in the prenatal and neonatal periods, but the microbiome after the age of 3 years tends to stabilize. At

every stage of life, the microbiota is susceptible to external pressures, diet or disease in the host, with constant metabolic and physical signaling occurring between microbes and host cells, not just among the microbes themselves.

2. An example of a determinant that is *not* known to be associated with variation in the composition of microbial communities at different sites is

- A. Colonic microbiota varying with colon cancer
- B. Vaginal microbiota varying with menses
- C. Periodontal microbiota varying with tooth brushing
- D. Gastrointestinal tract microbiota varying with diet
- E. Nasopharyngeal microbiota in young children varying with seasonal change

Answer: C Cooperative interactions between microbes and their hosts typically involve microbial participation in host functions such as defense, metabolism, and reproduction. All of the above except C are known to cause perturbations. Large perturbations, such as antibiotic exposure or enteric infections, can lead to transient disequilibria or even the development of new stable states.

3. For which of the following conditions does the presence of *Helicobacter pylori* alter the risk?

- A. Gastric cancer
- B. Peptic ulcer disease
- C. Reflux esophagitis
- D. Childhood-onset asthma
- E. All of the above

Answer: E In the absence of *H. pylori*, gastric microbiota diversity is high (although it was once believed that the stomach is sterile). In contrast, among *H. pylori*-positive individuals, this organism accounts for more than 90% of the sequence reads from gastric microbiota. The presence of *H. pylori* increases the risk for peptic ulcer disease, gastric cancer, and mucosa-associated lymphoid tissue (MALT) lymphomas. On the other hand, the absence of *H. pylori* increases the risk of reflux esophagitis and childhood-onset asthma. (See section on gastric microbiome under Disease Links and Health Implications.)

4. Which of the following disease links with gut microbiota is correct?

- A. Antibiotic use in infancy is associated with obesity development.
- B. Shifts in gut microbes in infancy play a role in causation of autism.
- C. Changes in gut microbiota are pathogenic in the early stages of systemic lupus erythematosus.
- D. Disturbances in the gut microbiome by chronic alcohol exposure contribute to development of alcoholic steatosis of the liver.
- E. None of the above

Answer: A Most microbiome associations with human disease have been observational in nature and therefore do not prove cause-and-effect relationships (see Cause or Effect?). Although a causal relationship cannot be considered definitive at this time, antibiotic use in human infancy, before the age of 6 months, has been significantly associated with later obesity development. Furthermore, perinatal administration of *Lactobacillus*-based probiotics has been shown to decrease excessive weight gain during childhood. These and other observations have suggested that early-life microbiota are modifiable, with alterations affecting the risk of childhood-onset obesity (see The Gut Microbiota and Obesity). At this point, associations between shifts in gut microbes and autism or alcoholic steatosis (although chronic alcohol exposure does alter the gut microbiome) are entirely observational and preliminary. Substantial alterations in the gut microbiota have been identified in patients with early rheumatoid arthritis, consistent with a pathogenic role, but not with systemic lupus erythematosus. (See corresponding sections under Disease Links and Health Implications.)

1. Which of the following host factors should be considered in selecting an antibiotic regimen for treatment of a patient?

- A. Prior history of allergies
- B. Whether the patient is currently pregnant or breast-feeding
- C. Age and sex of the patient
- D. Options A and B
- E. Options A, B, and C

Answer: E The need to consider host factors A and B is obvious. The age and sex of the patient are also relevant. Some antibiotics (e.g., fluoroquinolones, tetracyclines) are generally avoided in children with only a few exceptions. In clinical studies, young women were more likely to develop rash to gemifloxacin than were men or older women.

2. Important justifications for use of antimicrobial combinations in clinical practice include all of the following *except*

- A. To reduce drug toxicity by allowing use of half of the usual full doses of each of two agents
- B. To attain bactericidal synergism for treating enterococcal endocarditis
- C. To treat documented polymicrobial infections
- D. To minimize emergence of resistance to rifampin in treating prosthetic device infections
- E. To target a broader range of potential pathogens during empirical therapy

Answer: A Although using combinations to reduce doses of individual component drugs is a theoretically plausible consideration, it is not currently feasible to accomplish this in practice. Combinations are used to achieve bactericidal synergism to treat endocarditis (e.g., cell wall-active agent plus an aminoglycoside to treat endocarditis due to an enterococcus or a penicillin-nonsusceptible viridans streptococcus), to treat polymicrobial infections (e.g., vancomycin plus a carbapenem to treat infection due to both MRSA and extended-spectrum β -lactamase-producing Enterobacteriaceae), and to minimize resistance to rifampin for infections due to prosthetic devices such as heart valves and joint prostheses.

3. Which of the following statements about antimicrobial agents is true?

- A. Regardless of the antimicrobial used, administration by the intravenous route is always more effective when doses are given at least every 4 hours.
- B. Daptomycin is effective for treatment of community-acquired pneumonia if it is administered once daily.
- C. In this day and age, there is no role for intramuscular administration of antimicrobial agents.
- D. It is usually wise to measure serum bactericidal titers in treating endocarditis.
- E. None of the above

Answer: E Answer A might be relevant to agents such as β -lactams, the effectiveness of which depends on “time above the MIC,” but does not apply to agents such as fluoroquinolones or aminoglycosides. Answer B is incorrect because daptomycin is not indicated for treatment of bronchopneumonia, as it is inactivated by pulmonary surfactant. Answer C is also not correct. Benzathine penicillin and ceftriaxone are used intramuscularly for treatment of syphilis and gonorrhea, respectively, in the outpatient setting. Answer D cannot be justified either. Although studies have suggested that higher serum bactericidal titers correlate with cure in endocarditis, the correlation is imperfect, the results are not always reproducible, and the procedures are labor-intensive. For these reasons, this test is rarely used in clinical practice.

1. A 72-year-old man was admitted with exacerbation of his chronic obstructive pulmonary disease (COPD) symptoms and temperature of 38.3° C. His respiratory symptoms improved and he defervesced with antibiotics; but on his third hospital day, he became extremely agitated, requiring haloperidol, a major tranquilizer and central nervous system dopamine-depleting agent. Within hours his temperature rose to 42° C, and he developed muscle rigidity and dysautonomia. What is the most likely etiology of his worsening clinical picture?

- A. Aspiration pneumonia due to his agitated
- B. Pulmonary embolism
- C. COPD exacerbation
- D. Nosocomial infection
- E. Neuroleptic malignant syndrome due to haloperidol

Answer: E Temperatures exceeding 41° C are often due to drug-induced imbalance in thermoregulatory mechanisms and may cause direct cellular damage (Chapter 434).

2. A 46-year-old female immigrant had returned to her work as a day-care teacher for a month after visiting her family in Central America at Thanksgiving when she developed watery diarrhea. She was otherwise well and afebrile. Her complete blood count and electrolyte panel were normal. Several of her pupils had similar illness. What is the most likely etiology of her illness?

- A. *Plasmodium vivax* infection
- B. Traveler's diarrhea due to toxigenic *E. coli*
- C. Amebiasis
- D. Shigellosis
- E. Viral gastroenteritis

Answer: E No laboratory abnormalities accompany typical benign acute viral infections. The first consideration in evaluating such a patient is that an infection unrelated to travel is more likely to be the cause of the illness. Common viral respiratory infections and gastroenteritis are accompanied by temperatures below 102° F.

3. A 36-year-old man developed low-grade fever, sore throat, and a rash. He had pharyngeal erythematous-based vesicles and ulcerations as well as vesicles on his hands and palms, feet, and buttocks. His 2-year-old child was recovering from a similar illness. What is the most likely etiology of his illness?

- A. Epstein-Barr virus infection
- B. Herpes simplex virus infection
- C. Leptospirosis
- D. Lyme disease
- E. Enteroviral hand-foot-and-mouth disease

Answer: E See Tables 280-3 and 280-4. The presence of fever and rash involving the palms and soles allows considerable narrowing of the differential diagnosis.

4. For which of the following ambulatory adult patients should an antibiotic be prescribed?

- A. A 47-year-old woman with no underlying medical conditions who has had a persistent cough for 2 weeks.
- B. A 28-year-old woman with 10-day illness and now with unilateral face pain, maxillary toothache, and worsening symptoms after initial improvement.
- C. A 31-year-old woman with pharyngitis but no fever, tonsillar exudates, tender anterior cervical adenopathy, or cough.
- D. A 54-year-old man with no fever and prolonged coughing lasting 6 weeks.

E. A 65-year-old man with COPD and yellow-green mucopurulent discharge and no other new symptoms.

Answer: B See section on initial management of suspected infection in the ambulatory setting.

5. A 76-year-old woman admitted for community-acquired pneumonia, treated empirically with moxifloxacin, developed severe watery diarrhea, abdominal pain, fever, and leukocytosis (white blood cell count of 30,000) on day 4 of hospitalization. What is the likely etiology of her nosocomial infection?

- A. *C. difficile* infection
- B. Urinary tract infection
- C. Intravenous catheter-related infection
- D. *Legionella* infection
- E. Drug fever

Answer: A Toxin-producing *C. difficile* is the only significant nosocomial gastrointestinal infection seen in hospitalized patients.

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APPROACH TO FEVER AND SUSPECTED INFECTION IN THE COMPROMISED HOST

1. A patient who has an absolute neutrophil count below 500 cells/mm³ for 2 weeks after induction therapy for acute myelogenous leukemia is at increased risk for

- A. *E. coli* bacteremia from the gastrointestinal tract
- B. Influenza infection involving the upper respiratory tract
- C. Varicella-zoster virus reactivation
- D. Cytomegalovirus disease involving the lungs
- E. *Cryptococcus neoformans* meningoencephalitis

Answer: A These patients do not have increased risk for influenza involving the upper respiratory tract compared with the population in general but have increased risk for complications (such as pneumonitis). Answers C to E are correct only for people with advanced deficits in T-cell immunity.

2. Early antibiotic therapy would be appropriate before documenting a microbial diagnosis in

- A. A neutropenic patient who has developed fever, with normal hemodynamics
- B. A heart transplant patient who has a new left lower lobe consolidation, fever, and leukocytosis
- C. A kidney transplant patient with pyuria, fever, and elevated creatinine concentration
- D. None of the above
- E. All of the above

Answer: E These all outline high-risk situations in which empirical antibiotic therapy would be appropriate before documentation of disease to avoid rapid progression with sepsis.

3. A man presents with diffuse papular skin lesions 20 days after receipt of bone marrow transplantation, with fever. He has been receiving fluconazole, moxifloxacin, and acyclovir prophylactically. The least likely cause of his skin lesions is

- A. *Candida glabrata*
- B. Sweet's syndrome
- C. *Aspergillus fumigatus*
- D. Herpes simplex virus
- E. A vasculitic reaction to a drug

Answer: D Herpes simplex virus rarely disseminates to cause these types of skin lesions, especially in people receiving acyclovir.

4. People who have received tumor necrosis factor inhibitors as biologic therapy for an autoimmune disease have heightened risks for infections caused by which of the following?

- A. Viruses
- B. Bacteria
- C. Fungi
- D. All of the above
- E. None of the above

Answer: D Tumor necrosis factor inhibition may alter immune responses to multiple arms of the immune system.

5. What is the most likely cause of neutropenic enterocolitis that developed after receipt of cytotoxic therapy for acute myelogenous leukemia?

- A. Cytomegalovirus
- B. *Clostridium difficile*
- C. Norovirus
- D. Mixed anaerobic and aerobic bacteria
- E. Adenovirus

Answer: D These infections are typically caused by organisms that are “native” in the gastrointestinal tract during episodes of mucosal injury.

Ch / 282 PREVENTION AND CONTROL OF HEALTH CARE–ASSOCIATED INFECTIONS

1. What percentage of device- and procedure-associated health care– associated infections that occur in U.S. hospitals are potentially preventable?

- A. 0-15%
- B. 20-30%
- C. 40-50%
- D. 55-70%
- E. 85-100%

Answer: D A systematic review of published studies found that 55 to 70% of central line–associated blood stream infections, catheter-associated urinary tract infections, ventilator-associated pneumonia, and surgical site infections are preventable with the use of currently available evidence-based prevention strategies and technologies. Unfortunately, many of these strategies are not consistently implemented.

2. Bathing of intensive care unit (ICU) patients with chlorhexidine on a daily basis has been associated with which of the following outcomes?

- A. Reduction in MRSA-positive clinical cultures attributable to the ICU
- B. Reduction in overall blood stream infection rates in ICU patients
- C. Reduction in central line–associated blood stream infection rates in ICU patients
- D. Reduction in environmental contamination with VRE
- E. All of the above

Answer: E Several quasi-experimental studies and three cluster-randomized controlled trials have demonstrated the potential for daily bathing with chlorhexidine to reduce a variety of health care–

associated infection outcomes in ICU patients. This intervention has generally been well tolerated. Further study of the risk of development of chlorhexidine resistance among common health care–associated pathogens as the use of chlorhexidine becomes more common is warranted. Daily chlorhexidine bathing in other settings has not been subject to such extensive study, and thus the role of the horizontal infection control intervention in the non-ICU setting is not yet known.

3. The increased rates of morbidity and mortality associated with health care–associated infections caused by multidrug-resistant organisms (MDROs), compared with those caused by susceptible organisms of the same species, are likely due to all *except* which of the following?

- A. Greater virulence of antimicrobial-resistant organisms compared with antimicrobial-susceptible organisms
- B. Delays in initiating effective antimicrobial therapy
- C. The presence of more severe underlying disease in patients who develop MDRO infections
- D. The availability of only less effective or more toxic antimicrobial agents for treatment of some MDRO infections compared with agents available for the treatment of more susceptible organisms

Answer: A The higher rates of morbidity and mortality associated with MDRO infections, compared with infections caused by susceptible organisms of the same species, are likely to be multifactorial in nature. In general, however, MDROs are not more virulent than susceptible organisms of the same species.

4. Which of the following scenarios does *not* represent an avoidable health care–associated risk factor for health care–associated infection or MDRO acquisition?

- A. The presence of an indwelling urinary catheter in an otherwise healthy patient who underwent elective knee replacement surgery 2 days earlier
- B. Insertion of a central venous catheter for administration of cytotoxic chemotherapy
- C. Insertion of an indwelling urinary catheter to reduce the need for nursing assistance in a 73-year-old patient with urinary incontinence
- D. Administration of antimicrobial prophylaxis for 48 hours after an elective colectomy
- E. Continuation of empirically prescribed piperacillin-tazobactam therapy for a patient admitted in septic shock who has now demonstrated a clinical response to current therapy and from whom pan-susceptible *E. coli* has been isolated from blood and urine specimens obtained at the time of admission

Answer: B The appropriateness of indwelling invasive devices and ongoing antimicrobial therapy should be assessed on a regular (i.e., at least once daily) basis with discontinuation of the device when an appropriate indication is not present and adjustment of antimicrobial therapy based on the results of diagnostic testing and clinical assessments.

5. Recommendations for the prevention of central line–associated blood stream infections (CLABSI) include all of the following *except*

- A. Use of maximal barrier precautions during catheter insertion (e.g., use of a cap, mask, sterile gown, sterile gloves, and sterile full-body drape)
- B. Routine replacement of central venous catheters every 7 days
- C. Preparation of the catheter insertion site with an antiseptic agent (e.g., >0.5% chlorhexidine preparation with alcohol) before catheter insertion
- D. Daily review of catheter necessity with immediate removal of catheters that are no longer necessary
- E. Scrubbing of the access port with an antiseptic before accessing the port

Answer: B Currently available evidence-based guidelines for prevention of CLABSI provide recommendations for catheter insertion, use, and maintenance. Routine catheter replacement is not a recommended strategy for CLABSI prevention.

1. A 30-year old traveler to Goa, India, for vacation develops diarrhea and fever on the fifth day at the resort. After 36 hours of diarrhea, stools begin to contain bright red blood. She visited a U.S. travel medicine clinic before heading for India and was given two antibiotics, one for the common watery diarrhea and a second in the less likely event that she developed bloody diarrhea and fever. Which of the following antibiotics would she have correctly received from the clinic to treat dysenteric traveler's diarrhea?
 - A. Oral ciprofloxacin, 500 mg twice a day for 3 days
 - B. Azithromycin, 1000-mg single dose
 - C. Levofloxacin, 500 mg once a day for 3 days
 - D. Metronidazole, 500 mg three times a day for 10 days
 - E. Rifaximin, 200 mg three times a day for 3 days

Answer: B The invasive pathogens (*Shigella*, *Salmonella*, and *Campylobacter*) occur more commonly in travelers to Asia compared with destinations in Africa and Latin America. Ciprofloxacin and levofloxacin would not be the best choice in this patient because of the importance of fluoroquinolone-resistant *Campylobacter* as a causative agent of dysenteric traveler's diarrhea occurring in Asia. Metronidazole would be appropriate for persistent diarrhea caused by *Giardia* or *Entamoeba histolytica* but would not be useful in most patients with traveler's diarrhea where the typical enteropathogenic agents are bacterial in origin. Rifaximin is of value for the common watery diarrhea of travelers but is of no value for the treatment of mucosally invasive enteropathogens as the drug is poorly absorbed (<0.4%). Azithromycin has the broadest spectrum of activity against the causes of traveler's diarrhea and should be preferentially used for dysenteric traveler's diarrhea or when breakthrough diarrhea occurs in a patient taking rifaximin to prevent traveler's diarrhea.

2. Two families eat a common meal and five people from the two families develop diarrhea the next afternoon, of whom two are passing grossly bloody stools. A sixth person eating the meal without diarrhea develops motor weakness and decreased reflexes 11 days later, progressing to quadriplegia. She is confined to a hospital intensive care unit requiring mechanical ventilation. What probably caused the outbreak of diarrhea and the case of quadriplegia?
 - A. *Campylobacter jejuni*
 - B. *Shigella flexneri*
 - C. *Vibrio cholerae*
 - D. *Aeromonas sobria*
 - E. *Vibrio vulnificus*

Answer: A The most common causes of dysentery (passing grossly bloody stools) in the United States are *Shigella* and *Campylobacter*. *Campylobacter* is the most important definable cause of Guillain-Barré syndrome (GBS), occurring during the 2 months after *Campylobacter* infection in fewer than 2 per 10,000 cases. GBS is an example of molecular mimicry with antibodies directed to *Campylobacter* lipooligosaccharides and peripheral nerve gangliosides. The complication can occur in asymptomatic *Campylobacter* infection as was seen in this case. *Campylobacter* can be suspected by searching for serologic evidence of past infection in subjects with GBS.

3. You receive a call from your office. One of your patients has developed watery diarrhea 2 hours after eating at a local restaurant. No other persons are known to be ill. What should you tell your office?
 - A. Obtain a sample of food if possible for *S. aureus* enterotoxin.
 - B. Have the office draw a blood culture sample.
 - C. Do a complete clinical and epidemiologic history.
 - D. Recommend ciprofloxacin therapy for the patient.
 - E. Collect a stool sample for studies of enteric pathogens.

Answer: C A meal or beverage can be implicated as a cause of an enteric disease if there are associated cases of illness occurring with a common exposure. The only exception to this is a case of classic botulism occurring shortly after consumption of a food. The incubation period of an enteric infection/intoxication can be as long as 9 days and as short as 2 hours. Thus, the problem could have resulted with an exposure during this broad time range. By taking a careful history, it would have been learned that this patient had diarrhea as well as vomiting and a temperature of 102° F. By obtaining more information, an infectious agent is more likely than a preformed toxin of *Staphylococcus aureus* or *Bacillus cereus*, which could produce illness with this short incubation period. Clearly, the meal was not responsible because an enteric infection has a minimum incubation period of 14 hours. In this subject, a stool culture revealed a *Salmonella* spp, and he gave a history of eating a turkey meal the day before.

4. In January 2010, local authorities in Maryland were notified of a large cluster of gastroenteritis involving more than 100 persons, 24 to 36 hours after consumption of raw oysters in three Baltimore restaurants. The median incubation period was 30 hours. Vomiting and watery nonbloody diarrhea with abdominal pain were common. Some subjects complained only of nausea and vomiting. Fever was seen in approximately 30% of the affected persons. Approximately 20 subjects had stool studies performed, which were negative for bacterial and parasitic pathogens. Clinical recovery was complete in 72 hours, and there were no long-term sequelae. Which of the following organisms likely caused the outbreak?

- A. *Shigella sonnei*
- B. *Vibrio cholerae*
- C. *Giardia*
- D. Norovirus
- E. *Staphylococcus aureus* enterotoxin

Answer: D In the United States each year, more than 20 million cases of acute norovirus gastroenteritis occur, with half being reported to be food-borne. The reservoir of norovirus is infected persons who may be asymptomatic. With fecal contamination of an oyster bed, norovirus contamination occurs readily. Outbreaks of norovirus gastroenteritis from oysters are not rare. The illness seen here meets the Kaplan criteria for norovirus illness: (1) median duration of illness is 12 to 60 hours; (2) median incubation period is 24 to 48 hours; (3) more than 50% of affected persons complain of vomiting; and (4) no bacterial agent is found. Norovirus is more common in winter months, which fits with the timing of the outbreak. *Shigella*, *V. cholerae*, and *Giardia* produce a different disease (febrile dysentery, dehydrating diarrhea, persistent illness). *Staphylococcus* food poisoning associated with concentration of an enterotoxin in improperly handled food has a shorter incubation period (2 to 7 hours) and is not likely to be seen in oyster-associated outbreaks.

5. On June 15, 2010, local physicians reported 11 pediatric cases of diarrhea to a county health department. A preliminary investigation found that nine of the persons recently had visited a large city park with a wading pool. The health department performed an evaluation of persons who used the park or wading pool and found that of 89 children interviewed, 69 met the case definition. Secondary spread of illness to family members and contacts was found to be common. One third of the children had temperature above 102° F; half had bloody diarrhea. A pathogen was isolated from three children providing a stool sample. Which of the following is likely to be the cause of the outbreak?

- A. *Shigella sonnei*
- B. Enteroinvasive *E. coli*
- C. *Campylobacter jejuni*
- D. *Vibrio cholerae*
- E. Enterotoxigenic *E. coli*

Answer: A Outbreaks of infectious diarrhea have been reported among infants and children in wading pools where chlorine levels are not monitored and fecal contamination is expected. The likely causes of the illness are the low-dose pathogens: norovirus, *Shigella* spp, Shiga toxin–producing *E. coli*, *Giardia*, and *Cryptosporidium*. Secondary spread of enteropathogens commonly occurs only for low-dose organisms. *Salmonella* and *Campylobacter* in most patients (outside the very young infant stage) are moderate-dose pathogens. *V. cholerae* and ETEC are high-dose pathogens. The moderate- and high-dose pathogens would be rare causes of outbreaks in this setting and would not have been associated with secondary transmission. If Shiga toxin–producing *E. coli* (STEC) would have been given as an option, two answers could have been correct. STEC is a low-dose pathogen seen in wading pool outbreaks and with secondary cases. The high fever is more compatible with shigellosis than with STEC diarrhea, however. *V. cholerae*, EAEC, and ETEC are each high-dose pathogens not associated with wading pools; secondary spread does not occur for them, and none causes dysenteric illness.

Ch / 284 **APPROACH TO THE PATIENT WITH URINARY TRACT INFECTION**

1. A 32-year-old gravida 2 para 1 woman presents to the obstetric emergency department at 29 weeks' gestation with temperature of 39.2° C and right costovertebral angle pain and tenderness. There is associated vomiting; the blood pressure is stable. She has no history of prior urinary tract infection and has received no antimicrobial therapy during this pregnancy. Intravenous rehydration therapy is initiated, and blood and urine culture specimens are obtained. What is the most appropriate next step?

- A. Await results of cultures before initiating antimicrobial therapy.
- B. Initiate therapy with ciprofloxacin, 500 mg PO bid.
- C. Initiate therapy with ceftriaxone, 1 to 2 g IV q24h.
- D. Initiate therapy with levofloxacin, 750 mg IV q24h.
- E. Await results of computed tomography scan before initiating antimicrobial therapy.

Answer: C Pregnant women presenting with acute pyelonephritis at this time of gestation are at high risk for premature labor and delivery at a vulnerable stage for the fetus. Empirical antimicrobial therapy should be initiated promptly, and initial therapy should be parenteral. Fluoroquinolone antimicrobials are contraindicated for pregnant women because of concerns with fetal cartilage development. There is no suggestion from her history that she has an increased risk for a resistant organism, and parenteral ceftriaxone would be the treatment of choice. (Vazquez JC, Abalos E. Treatments for symptomatic urinary tract infections during pregnancy. *Cochrane Database Syst Rev*. 2011;1:CD002256.)

2. A 22-year-old woman presents to her family physician with a second episode consistent with acute cystitis in the past 6 months. The previous episode responded promptly to empirical short-term antimicrobial therapy. She is sexually active in a stable monogamous relationship. Empirical antimicrobial therapy is again prescribed for treatment of this episode. What additional advice should she be given with respect to behavioral modification to decrease her risk of subsequent recurrent infection?

- A. Ensure bladder voiding immediately after sexual intercourse.
- B. Discontinue use of spermicide birth control method.
- C. After bowel movements, she should wipe herself from front to back.
- D. Increase her intake of cranberry juice.
- E. Use showers rather than baths for personal hygiene.

Answer: B The only behavioral risk factor, other than sexual intercourse, that is modifiable is discontinuation of use of spermicide for birth control. Use of spermicide for birth control is associated with at least a two-fold higher risk for recurrent urinary tract infection in sexually active young

women. Whereas early studies suggested a modest benefit of cranberry capsules, more recent studies report no significant improvements with the use of cranberry products. The other interventions suggested have consistently been reported not to be associated with recurrent urinary tract infection. (Gupta K, Hooton TM, Naber KG, et al. Executive summary: international clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*. 2011;52:561-564; and Beerepoot MA, Geerlings SE, van Haarst EP, et al. Nonantibiotic prophylaxis for recurrent urinary tract infections: a systematic review and meta-analysis of randomized controlled trials. *J Urol*. 2013;190:1981-1989.)

3. A 42-year-old man with a high-level cervical spinal cord injury was admitted to the rehabilitation unit 2 weeks ago. There is an indwelling catheter in place for bladder management. He has a single temperature elevation to 38.2° C with no localizing findings. Complete blood count and urine and blood culture specimens are obtained. The white blood cell count was normal, and after 48 hours, the blood culture is negative but the urine specimen has returned growing *E. coli* of more than 108 CFU/mL and an enterococcus of more than 108 CFU/mL. He remains afebrile and otherwise stable. What is the appropriate approach to management at this time?
- A. Remove the indwelling catheter and begin intermittent catheterization for management of bladder emptying.
 - B. Obtain ultrasound and urodynamic studies to exclude urolithiasis.
 - C. Institute antimicrobial therapy for treatment of the organisms isolated from the urine culture.
 - D. No changes in management are required.
 - E. Request urologic consultation.

Answer: D This patient has a chronic indwelling catheter and will be bacteriuric at any time. Thus, the urine culture would be expected to be positive. In the absence of clinical evidence of infection, such as elevated white blood cell count or continuing fever, this is asymptomatic bacteriuria, and antimicrobial therapy is not indicated. It is desirable to remove the indwelling catheter as soon as possible, but in a patient with a high-level cervical spine injury, intermittent catheterization by the patient himself is unlikely to be feasible. All spinal cord-injured patients require urodynamic assessment, but this single fever and positive urine culture would not be an indication for evaluation outside normal management. (Nicolle LE. Urinary tract infections in special populations: diabetes, renal transplant, HIV infection, and spinal cord injury. *Infect Dis Clin North Am*. 2014;28:91-104.)

4. A 63-year-old man presents with temperature of 39.2° C associated with rigors; blood pressure is 70/40. He was diagnosed with a ureteric stone complicated by ureteric obstruction 36 hours previously and 12 hours before fever onset had successful endourologic intervention to extract the stone. The urine culture specimen collected before the procedure is growing *E. coli* of more than 108 CFU/mL, but susceptibilities are not yet available. Ciprofloxacin 500 mg PO bid had been initiated before the procedure. What is the appropriate approach at this time?
- A. Continue the ciprofloxacin initiated, pending susceptibility information.
 - B. Change to oral cefixime, 400 mg once daily, to cover potential resistant organisms.
 - C. Initiate broad-spectrum parenteral antimicrobial therapy effective for ciprofloxacin-resistant *E. coli* immediately.
 - D. Initiate antimicrobial therapy with gentamicin plus ampicillin to cover additional pathogens.
 - E. Give a bolus of normal saline and reassess the patient in 4 to 6 hours.

Answer: C This patient has a presumptive diagnosis of postsurgical sepsis. It is essential that effective antimicrobial therapy, together with other supportive therapy, be initiated immediately. When patients progress to septic shock, one variable associated with mortality is delayed institution of effective antimicrobial therapy. In this case, it is possible that the patient has a ciprofloxacin-susceptible organism and the obstruction prevented access of antimicrobial to the infected site. It is also possible that a new organism was introduced at the time of the surgical procedure. However, as the organism may be resistant to ciprofloxacin, broad-spectrum parenteral therapy to cover potentially resistant

organisms should be selected. This could be piperacillin-tazobactam or a carbapenem. Gentamicin and ampicillin are usually also reasonable choices. However, given the likelihood of resistant organisms, this regimen may not provide full coverage, and broader spectrum agents seem more appropriate. Blood and urine cultures should be repeated before initiation of the antimicrobial therapy. Obviously, the antimicrobial therapy should be reassessed and appropriate modifications made once the culture results and susceptibilities are available. (Nicolle LE. Urinary tract infection. *Crit Care Clin*. 2013;29:699-716.)

5. An 82-year-old woman with poorly controlled type 2 diabetes is admitted to the intensive care unit with respiratory failure complicating pneumococcal pneumonia. An indwelling urethral catheter was inserted for output monitoring on admission. Because of initial uncertainty about the etiology of her pneumonia, she was treated empirically with broad-spectrum therapy of meropenem and azithromycin. These have been continued, despite *S. pneumoniae* isolated in blood cultures being susceptible to penicillin G. Seven days after admission, the urine is observed to be cloudy, and the nurse sends a urine specimen for culture. It returns with a report of isolation of *Candida albicans* of more than 10⁸ CFU/mL. The patient is afebrile and, while still requiring ventilatory support, is showing improvement in oxygenation. What is the appropriate response to the urine culture report?
- A. Institute fluconazole 400 mg once daily for *Candida* urinary tract infection.
 - B. Obtain a blood culture sample for yeast species.
 - C. No interventions are required.
 - D. Review the need for the indwelling catheter and remove it if possible.
 - E. Repeat the urine culture to confirm *Candida* funguria.

Answer: D This patient has diabetes, is receiving broad-spectrum antimicrobial therapy, and has an indwelling catheter in situ. These are the three most important risk factors for acquisition of candiduria. There is no clinical evidence to suggest symptomatic infection from a urinary source. The diagnosis is asymptomatic candiduria, and antifungal treatment is not indicated. For any patient with an indwelling urethral catheter, the need for continuing use of the catheter should be reassessed on a daily basis and the catheter removed as soon as it is no longer necessary to limit development of complications. If the indwelling catheter cannot be removed in this patient, there is no indication for other interventions relevant to the candiduria as long as the patient is clinically improving. (Kauffman CA. Diagnosis and management of fungal urinary tract infection. *Infect Dis Clin North Am*. 2014; 28:61-74.)

Ch / 285 **APPROACH TO THE PATIENT WITH A SEXUALLY TRANSMITTED INFECTION**

1. The Centers for Disease Control and Prevention has recommended gonorrhea treatment with an injectable third-generation cephalosporin and azithromycin. Which of the following answers is the correct rationale for this recommendation?
- A. Azithromycin should be used in conjunction with an injectable third-generation cephalosporin to provide therapy with two different mechanisms of action, thereby delaying emergence of resistance.
 - B. There is a high rate of concomitant chlamydial infection as well as an increasing recognition of *Mycoplasma genitalium* coinfection that should be treated.
 - C. Cefixime and azithromycin may be used in some settings without further follow-up.
 - D. Moxifloxacin may be used to treat *M. genitalium* as well as *Neisseria gonorrhoeae*.

Answer: A A theoretical basis does exist for using two antimicrobials with different mechanisms of action to treat gonorrhea and to prevent emergence of resistance. Although there is a high rate of concomitant chlamydia and mycoplasma coinfection with gonorrhea, it does *not* reflect the rationale for using azithromycin and an injectable third-generation cephalosporin as first-line therapy against

gonorrhea. Oral cefixime therapy is a second-line therapy and should be followed with a test of cure. Fluoroquinolones are to be avoided for gonorrhea.

2. Male circumcision is currently recommended by WHO/UNAIDS. Which of the following statements is *incorrect* regarding male circumcision?

- A. The long-term effectiveness of male circumcision is well described and has been demonstrated in several studies.
- B. Sexually transmitted infection (STI) prevention trials that incorporate interventions like circumcision may lead to a bias/blunting of effect compared with community standards of care.
- C. Male circumcision demonstrated greater than 75% reduction in human immunodeficiency virus (HIV) acquisition during a 5-year period in at least two African trials.
- D. Circumcision was not accepted by men after completion of the trial.
- E. Circumcised men were more likely to engage in risky sexual behaviors compared with uncircumcised men.

Answer: C The uptake of circumcision after the trial approached 80% in the Rakai study. Long-term effectiveness of circumcision has not been *proved* but may be inferred from several studies. In larger randomized controlled trials, circumcision compared with community standard of care did not appear to have a biased effect. Further, in the post-trial surveillance for the Rakai study, there were no statistically significant differences in sexual risk-taking behaviors in men subsequently choosing circumcision compared with those who did not choose circumcision, and there were no statistically significant differences in sexual risk-taking behavior in uncircumcised versus circumcised men.

3. Human papillomavirus (HPV) is a vaccine-preventable STI. Which of the following is true about HPV vaccination?

- A. Oral HPV-associated head and neck cancers (associated with smoking, male gender, and HIV infection) can be prevented with vaccination.
- B. Two vaccines are currently available. Both protect against HPV types 16 and 18, which are responsible for at least 85% of all cervical neoplasia; one of the vaccines includes types 6 and 11 (responsible for most cases of genital warts and precancerous anal lesions).
- C. Papanicolaou smears are recommended for all sexually active women beginning at coitarche, and HPV testing is recommended for women younger than 30 years.
- D. The quadrivalent HPV vaccine protects against only genital warts in males.

Answer: B Two vaccines are currently available. Both protect against HPV types 16 and 18, which are responsible for at least 85% of all cervical neoplasia; one of the vaccines includes types 6 and 11 (responsible for most cases of genital warts and precancerous anal lesions). Current HPV vaccines have not been shown to have any effect on head and neck cancers. The quadrivalent vaccine does protect against anal precancers and may influence future vaccine recommendations.

4. Which of the following are true about vaginal discharge and syndromic STI treatment?

- A. Vaginal-associated and cervical-associated causes of vaginal discharge are difficult to discriminate on the basis of symptoms alone.
- B. Many STIs in females are asymptomatic, leading to underidentification and undertreatment.
- C. Subclinical STI may still contribute significantly to genital inflammation and risk of HIV transmission and acquisition.
- D. All women possess a similar vaginal milieu that contributes significantly to bacterial vaginosis, a common noninfectious cause of vaginitis.
- E. A, B, and C are true.

Answer: E All of the responses are true *except* D. Women possess a heterogeneous vaginal microbiome, some species of which are associated with an increased risk of bacterial vaginosis. Mlisana and coworkers demonstrated elevated cervicovaginal cytokine levels for women with STI, regardless of

self-report of vaginal discharge. Vaginal discharge has poor sensitivity, specificity, and positive predictive value as a marker for STIs.

5. Many commercial laboratories have switched to use of treponemal-specific tests for syphilis diagnosis. Which of the following statements is true regarding the “reversed” testing algorithm?

- A. Treponemal-specific testing may be used to follow treatment.
- B. Some larger commercial laboratories have reversed the order of testing, using an antitreponemal test followed by an anticardiolipin test, which allows automation and may be cost-effective in areas of low endemicity.
- C. If a patient has a positive treponemal antibody test result and a negative serologic test result, that patient has a false-positive syphilis test result and does not require treatment.
- D. A patient presents with a positive treponemal test result and elevated serologic (1 : 64) titer 9 months ago. He was treated appropriately and lost to follow-up. The patient now presents with a positive treponemal test result and a nonreactive serologic test result. This patient should be retreated.

Answer: B Treponemal-specific tests are not used to follow treatment. Non-treponemal-specific antibody tests (e.g., VDRL, RPR) should still be used to monitor therapy; specifically, a four-fold decrease in titer indicates adequate treatment. A patient with a positive treponemal antibody test result and a negative serologic test result may have old or untreated syphilis. If a false positive is suspected, a second treponemal antibody test should be performed. This patient has evidence of appropriately treated syphilis (as evidenced by a greater than four-fold decrease in titer to a nonreactive serologic test) and does not require further therapy.

Ch / 286 **APPROACH TO THE PATIENT BEFORE AND AFTER TRAVEL**

1. A tourist visiting Burkina Faso (West Africa) for 1 week during the dry season (December to June) should receive which of the following vaccines?

- A. Plague
- B. Cholera
- C. Hepatitis C
- D. Meningococcal
- E. Japanese encephalitis

Answer: D Burkina Faso is in the meningitis belt of Africa. There is no plague vaccine currently and no risk to routine tourists in Africa. Cholera vaccine is indicated only for aid and refugee workers. Japanese encephalitis occurs only in Asia.

2. A traveler to Lake Titicaca (3800 m) in Bolivia should consider pre-ascent prophylaxis with

- A. Ibuprofen
- B. Acetazolamide
- C. Prednisone
- D. Furosemide
- E. Isosorbide dinitrate

Answer: B Acetazolamide hastens acclimatization by causing a bicarbonate diuresis and metabolic acidosis. Ibuprofen can prevent altitude headache but has no effect against more serious altitude manifestations. Dexamethasone but not prednisone can be used to treat but not to prevent cerebral edema. Furosemide has no effect against high-altitude pulmonary edema and does not prevent it. Nitrates are ineffective against the increased pulmonary artery pressures induced by altitude.

3. The most common vaccine-preventable disease of travelers is

- A. Hepatitis A
- B. Typhoid
- C. Yellow fever
- D. Influenza
- E. Measles

Answer: D Studies indicate that up to 2% of all travelers acquire influenza during their trip. This is orders of magnitude more common than the risk of the other diseases listed.

4. Acute diarrhea occurs disproportionately in travelers returning from which region?

- A. Africa
- B. South America
- C. South Central Asia
- D. China
- E. Caribbean

Answer: C Epidemiologic evidence from the GeoSentinel network is described in the text and can be found in reference 1.

5. Travelers should be instructed to avoid what exposure in areas that are endemic for schistosomiasis?

- A. Recreational (swimming, rafting, wading) or other exposure to fresh water
- B. Eating of unpasteurized dairy products
- C. Caves
- D. Undercooked shellfish
- E. Ticks

Answer: A Schistosomiasis is acquired when larvae that are harbored by freshwater snails are excreted into lakes, rivers, streams, or ponds and penetrate the skin of the traveler.

Ch / 287 **ANTIBACTERIAL CHEMOTHERAPY**

1. For β -lactam antibiotics, the index that is most closely linked to the ability of the drug dose and schedule to kill the target pathogen is

- A. Free drug C_{max}/MIC ratio
- B. Free drug AUC/MIC ratio
- C. Time (fraction of a dosing interval) that free drug concentrations exceed the MIC
- D. Total drug AUC/MIC ratio

Answer: C β -Lactam drugs are not particularly concentration dependent in their rate of kill and reach a maximal kill rate at low multiples of the MIC (usually around four-fold). Except in unusual circumstances, there is little in the way of persistent microbiologic effect after drug concentrations at the infection site decline below the MIC. Consequently, the ability to kill target pathogens is increased as time of free drug exceeding the MIC increases. Again, in the majority of instances, only free (non-protein bound drug) is microbiologically active.

2. In choosing an optimal drug dose and schedule for a patient's serious infection, which of the following is the most important consideration?

- A. MIC of the pathogen
- B. Drug dose chosen
- C. Protein binding of the antibiotic chosen
- D. Site of infection
- E. Toxicity profile of the drug chosen
- F. All of the above

Answer: F There are a small number of factors that clinicians can control that have an impact on the ability of a chosen drug dose and schedule to help a patient recover from an infection. Knowledge of the MIC of the infecting pathogen is critical as irrespective of the drug chosen, a lower MIC value will give a higher probability of attaining the target for a good therapeutic outcome. Likewise, the drug chosen has properties that may help or hinder in a specific case. For example, an agent that is not bactericidal is not likely to be an optimal choice in a patient with meningitis. As part of this, only free drug is (in the main) microbiologically active, so this is a serious consideration. The dose size and frequency will have a direct impact on the likelihood of achieving an exposure target that will optimize the likelihood of a good outcome. Understanding the probable infection site is important as penetration will be different into skin, cerebrospinal fluid, epithelial lining fluid, and prostate. Finally, the toxicity profile is important. Choosing a nephrotoxic agent for an intensive care unit patient would be improvident, unless there was little alternative. Consequently, all of the factors need to be considered by the clinician.

3. Which of the following is most important for resistance emergence?

- A. Mobile genetic element
- B. Efflux pump upregulation
- C. Drug-inactivating enzymes (like β -lactamases)
- D. None of the above
- E. All of the above

Answer: E Each of these represents a way for the infecting pathogen to increase survivorship in the face of antimicrobial therapy. In A and C, there is most often a destruction of the drug. In B, the drug that does penetrate into the organism is actively pumped out, lowering the drug concentration below the critical level necessary for organism kill. These mechanisms also may interact with each other.

4. Of the drugs listed, which are nephrotoxic?

- A. Linezolid
- B. Vancomycin
- C. Meropenem
- D. Gentamicin
- E. B and D
- F. All of the above

Answer: E The nephrotoxic potential of aminoglycosides (e.g., gentamicin, tobramycin, amikacin) has been known for decades. Only more recently have we come to understand that higher doses of vancomycin (>2 g/day) are associated with a substantial risk of nephrotoxicity. (Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses are associated with an increased incidence of nephrotoxicity. *Antimicrob Agents Chemother.* 2008;52:1330-1336; and Lodise TP, Patel N, Lomaestro B, et al. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. *Clin Infect Dis.* 2009;49:507-514.

5. Which of the following patients is likely to have the highest antimicrobial drug clearance (and hence lowest levels of the antibiotic)?
- A. A 70-year-old woman with hospital-acquired pneumonia caused by an organism carrying a carbapenem-resistant Enterobacteriaceae
 - B. A 20-year-old patient who has crashed his Kawasaki Ninja into a tree, causing head injury, and who has developed a ventilator-associated pneumonia caused by *Pseudomonas aeruginosa* and is septic
 - C. A 50-year-old diabetic man with an infected foot ulcer
 - D. A 30-year-old sexually active woman with an uncomplicated urinary tract infection
 - E. A 40-year-old man with a pneumococcal superinfection after having developed an influenza virus infection (he did not get the vaccine)

Answer: B Most people think that seriously ill intensive care unit patients will, of necessity, have lower drug clearances because of illness. However, in this case, the young age of the patient, coupled with the sepsis, which will give him a hyperdynamic state, puts him at highest likelihood for having a very high drug clearance. Whereas many ascribe this to change in glomerular filtration rate (e.g., such a patient may have an estimated glomerular filtration rate in excess of 150 mL/minute), the hyperdynamic state also increases blood flow to other clearing organs, such as the liver, so even agents like a glycylicline (e.g., tigecycline), which are not heavily renally cleared, can have very high clearances. Such patients have been shown to have a high rate of failure in clinical trials. (Ambrose PG, Bhavnani SM, Ellis-Grosse EJ, Drusano GL. Pharmacokinetic-pharmacodynamic considerations in the design of hospital-acquired or ventilator-associated bacterial pneumonia studies: look before you leap! *Clin Infect Dis*. 2010;51[Suppl]:S103-S110.)

Ch / 288 STAPHYLOCOCCAL INFECTIONS

1. Ms. A is a 53-year-old woman admitted 1 week ago for fevers to 102.3° F and right flank pain. A computed tomography scan showed findings consistent with a 6-cm psoas abscess. Three blood culture samples were drawn, and empirical therapy was begun with vancomycin and piperacillin-tazobactam. All three blood culture samples grew methicillin-resistant *Staphylococcus aureus* (MRSA) with a vancomycin minimal inhibitory concentration (MIC) of 2 µg/mL. Treatment was de-escalated to vancomycin alone with documented trough concentrations of 15 µg/mL. One of two blood culture samples obtained on day 5 of therapy because of recurrent fever now is reported as positive for gram-positive cocci in clusters. Which of the following is the *most likely* explanation for the persistently positive blood culture?
- A. Vancomycin-nonsusceptible MRSA strain
 - B. Failure to obtain a transesophageal echocardiogram
 - C. Undrained psoas abscess
 - D. Subtherapeutic levels of vancomycin
 - E. Contamination of the blood culture sample with coagulase-negative staphylococci

Answer: C An isolate with a vancomycin MIC of 2 µg/mL is considered to be susceptible. Vancomycin-intermediate strains have low prevalence, 1 to 3%, and the MIC of these strains is 4 to 8 µg/mL. Vancomycin-resistant strains (MIC > 8 µg/mL) are rare. Thus, vancomycin nonsusceptibility is very unlikely. The vancomycin trough is in the therapeutic range, and although an echocardiogram is recommended for patients with complicated bacteremia, failure to obtain this study has not been shown to affect outcome. It is a mistake to attribute a positive blood culture to a contaminant in a patient with known *S. aureus* bacteremia. Poor source control with an undrained abscess, a well-known cause of persistent bacteremia, is the best answer.

2. Ms. B is a 58-year-old patient with degenerative arthritis who had a right hip replacement performed 3 weeks ago. She presents with about a week of slowly worsening hip pain with breakdown of the surgical site, cultures of which grew methicillin-susceptible *S. aureus*. Blood cultures are negative, and she has no fevers. She is adamant that she does not want the hardware removed. What is the best course of action in this situation?

- A. Begin oral cephalexin and discharge the patient for follow-up in 2 weeks to see if she improves.
- B. Begin a 2 week course of once-daily IV daptomycin and discharge the patient for follow-up in 2 weeks to assess need for further therapy.
- C. Treat her with cefazolin for a week, and if she does not get better, perform incision and drainage.
- D. Tell her that with incision, drainage, and debridement and a course of IV and oral antibiotics, she should do well without removal of the hardware.
- E. Try to convince her to have the hardware removed because if it is left in place, the infection cannot be cured.

Answer: D The patient is likely to have a methicillin-susceptible infection of the prosthesis. Because the infection is within a month of implantation and she has had less than 3 weeks of symptoms, she should do well with incision and drainage and a prolonged course of IV and oral antibiotics (3 to 6 months). Because hardware removal is probably not necessary, trying to threaten her into a procedure she has already said she does not want is unwise. Empirical therapy with an oral (A) or parenteral (C) β -lactam is ill-advised because it is important to document whether the joint is involved and to perform incision and drainage to minimize the possibility of progression of infection and a worse outcome. Empirical therapy with daptomycin is a poor choice for the same reasons, and moreover, a β -lactam is the preferred initial therapy for methicillin-susceptible *S. aureus* (MSSA).

3. Mr. C is a previously healthy 23-year-old man who is admitted with a 1-week illness characterized by a dry cough, fever, and myalgias. Yesterday he noticed that the cough became productive of yellow sputum, and last night he noticed shortness of breath. On examination, his temperature is 104° F, pulse is 128, respiratory rate is 22, blood pressure is 100/60, and pulse oximetry is 80% saturation on room air. He has rales at the right base, and a chest radiograph shows a fluffy right lower lobe infiltrate. A rapid influenza test result is positive, and sputum Gram stain shows numerous polymorphonuclear leukocytes and a few gram-positive cocci in clusters. Two blood culture samples are obtained. Which one of the following antibiotics is the worst choice to treat this suspected pneumonia?

- A. Clindamycin
- B. Ceftaroline
- C. Daptomycin
- D. Linezolid
- E. Vancomycin

Answer: C This patient has *S. aureus* pneumonia as a complication of influenza. The susceptibility of the organism is unknown, but he is at risk for MRSA infection. Either linezolid or vancomycin would be an appropriate choice as both are first-line agents. Of the three other antibiotics, all have issues, but daptomycin is the worst choice of the three because it is inactivated by pulmonary surfactant, resulting in treatment failure, and it is not indicated for treatment of pneumonia. Clindamycin could be used because most community MRSA and MSSA strains are susceptible, and although it is not a first-line agent in adults, it has been used to treat children with staphylococcal pneumonia. Ceftaroline, although not approved by the Food and Drug Administration for staphylococcal pneumonia, has an indication for treatment of community-acquired pneumonia, and it is active against both MRSA and MSSA. Thus, in a pinch, either clindamycin or ceftaroline would be preferred to daptomycin.

4. Mr. T is a 38-year-old diabetic patient who presents with a 2-day history of worsening pain and swelling of his left upper arm and subjective fevers. He tells you that he is penicillin allergic. His temperature is 99.8° F, and other vital signs are normal. On physical examination, there is a 5-cm-diameter tender, red, indurated lesion with central fluctuance over the triceps area. You perform incision and drainage, which yields about 3 mL of pus. Which one of the following antibiotics should *not* be used as empirical therapy for this community-acquired skin abscess?

- A. Clindamycin
- B. Doxycycline
- C. Levofloxacin
- D. Minocycline
- E. Trimethoprim-sulfamethoxazole

Answer: C Clindamycin, doxycycline, minocycline, and trimethoprim-sulfamethoxazole are active in vitro against both MRSA and MSSA strains and have been recommended and used to treat skin and soft tissue infections in areas with high prevalence of MRSA. Many MRSA strains and some MSSA strains are fluoroquinolone resistant, and therefore fluoroquinolones should not be used in the absence of documented in vitro susceptibility.

5. Which one of the following measures is probably the most effective means of preventing MRSA transmission?

- A. Chlorhexidine bath
- B. Good hand hygiene
- C. Isolation
- D. Mupirocin nasal ointment
- E. Screening for colonization

Answer: B Although randomized, controlled trials are lacking, on the basis of the known mechanisms of *S. aureus* transmission, whether MRSA or MSSA, good hand hygiene is probably the most effective strategy to prevent spread of the organism. Chlorhexidine baths alone have not proved effective. Screening and isolation of patients have had variable success. Mupirocin nasal ointment alone may reduce the risk of perioperative infection in colonized individuals but has not been shown to prevent transmission. The study of Huang and colleagues^{A6} found that in an intensive care unit setting, screening and isolation and targeted MRSA decolonization were relatively ineffective in reducing MRSA rates, whereas universal decolonization did reduce rates.

Ch / 289 **STREPTOCOCCUS PNEUMONIAE INFECTIONS**

1. Pneumonia can be caused by a variety of mechanisms. The pathobiology of pneumococcal pneumonia initially depends on

- A. colonization and inhalation of the organisms.
- B. inhalation of the organisms.
- C. colonization and aspiration of the organisms.
- D. aspiration of the organisms.
- E. spread from adjacent pleural spaces.

Answer: C The pathobiology of pneumococcal pneumonia initially depends on colonization and aspiration of the organisms. The “ecologic niche” of *Streptococcus pneumoniae* is the nasopharynx, and 20% of even healthy adults may carry the organism. Carrier rates are highest in late fall to early spring. Pathogens such as bacteria, viruses, and fungi can gain access to the lower respiratory tract and the distal airways by a number of mechanisms, including inhalation, aspiration (both gross and silent), spread from adjacent sites, and rarely by direct instillation as may occur with penetrating trauma. After colonization is established, the most common means of gaining access to the lower

airways is by aspiration of the pneumococcus. This can occur even during deep sleep in normal individuals. One does not have to have a seizure or be drunk and vomiting for this to happen. Pneumococcal virulence factors can influence both the colonization process and any subsequent bacterial invasion that may occur.

2. Mr. S is a 46-year-old man in excellent general health. He has no known medical problems and is a nonsmoker, a social drinker, and an avid jogger. He noted the onset of a cough productive of purulent sputum with occasional traces of blood, some right-sided pleuritic type chest pain, and shortness of breath even while walking over the past several days. He has also experienced some chills and sweats in the last day or 2. On examination, he is febrile, his respiratory rate is 24 breaths/min, and his chest radiograph shows a right middle lobe lobar consolidation without an effusion. His white blood cell count is 16,000 with a left shift, and a Gram stain of sputum showed classic gram-positive lancet-shaped diplococci with numerous polymorphonuclear leukocytes in the field. No other organisms were noted. A decision is made to admit him to the hospital. He has no drug allergies. Treatment should be started with

- A. a macrolide.
- B. penicillin.
- C. a fluoroquinolone.
- D. ceftriaxone.
- E. macrolide plus ceftriaxone.

Answer: B Treatment should start with penicillin. Unfortunately, the information gained from the history, physical examination, and chest radiograph are not necessarily definitively helpful in accurately predicting the etiologic pathogen. In this case, it certainly sounds as though a diagnosis of pneumonia is correct (if pulmonary embolism has been ruled out), there are no obvious risk factors for pathogens such as *Legionella* spp., and gram-negative rods would be quite unlikely. The finding of gram-positive cocci consistent with the pneumococcus and the absence of any other pathogen seen on Gram stain argues for a pneumococcal etiology. Given his overall presentation and the results obtained so far, it would be reasonable to begin treatment with a penicillin. He does not have risk factors for drug-resistant *Streptococcus pneumoniae* (DRSP), such as recent antibiotic treatment, age older than 65 years, HIV infection, or recent hospitalization, and he does not live in an area where DRSP is endemic.

Having said this, some would argue that overall, it might be safer to initiate treatment with a macrolide and a nonpseudomonal third-generation cephalosporin or a fluoroquinolone alone for a patient requiring admission to the hospital, but not the intensive care unit. As soon as specific culture data become available (e.g., blood or sputum), treatment could be changed to penicillin. Given the specifics of this case, however, it certainly is reasonable to initiate treatment with penicillin alone.

Mandell LA, Wunderlink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007; 44(Suppl):S27-S72.

3. A 20-year-old man who is in excellent health with no prior medical illnesses is involved in an accident while riding his motorcycle. He fractures his left femur and requires open reduction and internal fixation plus a splenectomy for his ruptured spleen. What would be the best way to prevent pneumococcal infection in this young man for the future?

- A. Daily low doses of penicillin orally
- B. Monthly intramuscular benzathine penicillin
- C. Pneumococcal polysaccharide vaccine
- D. Pneumococcal conjugate vaccine
- E. Pneumococcal conjugate vaccine followed by pneumococcal polysaccharide vaccine

Answer: E Pneumococcal conjugate vaccine followed by pneumococcal polysaccharide vaccine would be used to prevent pneumococcal infection. There are currently two types of pneumococcal vaccines,

a polysaccharide vaccine (PSV) and a protein conjugate vaccine (PCV). A vaccine would be the preferred method of protection by inducing immunity as opposed to relying on the use of prophylactic antibiotics. The problem is that in the case of a PSV, those who are immunosuppressed because of illness such as myeloma or lymphoma, immunosuppressing drugs, or transplantation are less likely to benefit from it. This includes patients who are either functionally or anatomically asplenic. For this 20-year-old accident victim who has never been given a pneumococcal vaccine before and is now at risk of pneumococcal infection because of his asplenic condition, he should be given a single dose of PCV13 followed at least 2 months later by a dose of PSV.

Musher D. How effective is vaccination in preventing pneumococcal disease? *Infect Dis Clin North Am.* 2013;27:229-241.

4. To diagnose pneumonia in general and pneumococcal pneumonia specifically, the best test is

- A. bronchoscopy.
- B. chest radiography.
- C. urinary antigen.
- D. biomarkers.
- E. none of the above.

Answer: E Unfortunately, there is no one specific test that is definitively diagnostic of pneumonia and pneumococcal pneumonia. The diagnosis is made by taking a careful history, doing a physical examination, and then supplementing this with additional tests depending on the severity of illness and whether or not admission to the hospital is being considered. Chest radiography is usually the most helpful because if the results are negative, it usually tends to rule out pneumonia. The constellation of findings obtained from the history, physical examination, and radiography can certainly suggest pneumonia versus some other process such as pulmonary embolism, but they are not foolproof, and the pattern of infiltrate on radiographs does not signify a particular pathogen. Initial treatment can be started with broader spectrum agents and then modified depending on any additional information that becomes available (e.g., cultures of blood or sputum, urinary antigen test results).

5. Pneumococcal resistance to penicillin is the result of

- A. a change in penicillin-binding proteins (PBPs).
- B. an antibiotic pump mechanism.
- C. an alternative metabolic pathway for the bacteria.
- D. mutations in the *gyrA* or *parC* genes.
- E. impaired access to the bacteria because of porin closure.

Answer: A Bacteria can protect themselves from antibiotics in a number of ways. To be effective, the antibiotic must be able to reach the target site within the pathogen, but this can be prevented by several mechanisms. These include:

1. An enzyme that inactivates the antibiotic
2. Decreased access to the bacterium via porin channels
3. Altered target sites so the antibiotic cannot recognize the target
4. Alternate metabolic pathways for the bacteria
5. Efflux pumps

In the case of β -lactam drugs such as the penicillins and the pneumococcus, the target sites are the penicillin-binding proteins, which are trans and carboxypeptidase enzymes involving bacterial cell wall synthesis. As the affinity of the drug for the target site decreases, it becomes harder for the drug to interact with the target and to induce any damage in the bacterial pathogen.

1. Group A streptococcus (GAS) is a major cause of pharyngitis and reasons for visits to health care facilities and for the prescription of antibiotics. Which of the following statements is correct?
- A. The treatment of GAS pharyngitis is an important strategy for the prevention of rheumatic heart disease in developed countries.
 - B. Periarticular findings, such as tenosynovitis, have not been considered to be part of the clinical spectrum of acute rheumatic fever but have been described with poststreptococcal reactive arthritis.
 - C. Penicillin treatment of the antecedent streptococcal infections is highly efficacious in preventing acute rheumatic fever and post-streptococcal glomerulonephritis (PSGN).
 - D. Quantitation of GAS from the throat swab culture can be used to differentiate carriage from infection.
 - E. On clinical grounds, streptococcal pharyngitis cannot be strongly suggested by the presence of fever, tonsillar exudate, tender enlarged anterior cervical lymph nodes, and presence of cough without laboratory confirmation.

Answer: B The term *poststreptococcal reactive arthritis* was first used to describe patients with arthritis after documented GAS infection but who failed to meet the Jones criteria for the diagnosis of acute rheumatic fever. Since then, the differentiation of PSRA from acute rheumatic fever has remained unsettled. In the latter half of the 20th century, rheumatic fever receded as an important health problem in almost all wealthy countries. Most of the reduction is attributable to improved living conditions, which have resulted in less overcrowding and better hygiene, with consequent reductions in transmission of GAS, not the widespread use of antibiotics. In other words, rheumatic fever is a disease of poverty. Studies carried out during epidemics of nephritis found that prior antibiotics had little, if any, effect in preventing acute PSGN. Penicillin is, nevertheless, effective in epidemiologic attempts to eradicate nephritogenic strains by treatment of acute glomerulonephritis patients and their colonized family contacts. Quantitation of GAS from the throat swab culture is unable to differentiate at presentation between a child who is acutely infected and one who is a chronic carrier presenting with acute nonstreptococcal pharyngitis. The methods for making that discrimination (testing for serological response and strain typing) require time and the aid of reference or research laboratories. A position paper by the American College of Physicians–American Society of Internal Medicine/American Academy of Family Physicians/U.S. Centers for Disease Control and Prevention recommends a departure from the principle of laboratory confirmation of all adult cases with recommendations to use a clinical prediction rule.

2. Acute rheumatic fever is a delayed, nonsuppurative sequela of a pharyngeal infection with group A streptococci (GAS). Which of the following statements is correct?
- A. Only “rheumatogenic” strains have been associated with acute rheumatic fever.
 - B. According to revised Jones criteria, the diagnosis of rheumatic fever can only be made when two of the major criteria or one major criterion plus two minor criteria are present along with evidence of streptococcal infection.
 - C. Penicillin (either oral penicillin V or injectable benzathine penicillin) is the treatment of choice.
 - D. Poststreptococcal reactive arthritis (PSRA) is an entity in patients who had arthritis after an episode of GAS pharyngitis but lacked other major criteria of acute rheumatic fever. However, they frequently go on to develop acute rheumatic fever.

Answer: C Penicillin is cost effective, has a narrow spectrum of activity, and has long-standing proven efficacy. In addition, GAS resistant to penicillin has not been documented. For penicillin-allergic individuals, acceptable alternatives include a narrow-spectrum oral cephalosporin, oral clindamycin, or various oral macrolides. Although the observation in some studies that only a few M serotypes (types 3, 5, 6, 14, 18, 19, 24, and 29) were implicated in outbreaks of rheumatic fever suggested a particular “rheumatogenic” potential of certain strains of GAS, the issue of potential rheumatogenic strains remains unresolved. A streptococcal strain capable of causing a well-documented pharyngitis almost always is potentially capable of causing rheumatic fever. Exceptions are chorea and indolent

carditis, each of which by itself can indicate rheumatic fever. Compared with acute rheumatic fever, the arthritis of PSRA is more likely to occur within 10 days after infection, be symmetrical and nonmigratory, last longer than 3 weeks, and be poorly responsive to aspirin or other nonsteroidal anti-inflammatory drugs. Periarticular findings, such as tenosynovitis, have not been considered to be part of the clinical spectrum of acute rheumatic fever but have been described with PSRA. Because a small proportion of patients with PSRA have been reported to develop subsequent valvular heart disease, these patients should be observed carefully for several months for clinical evidence of carditis.

3. The current recommendations for the surgical treatment of group A streptococci (GAS) necrotizing fasciitis are based on

- A. Prospective randomized controlled trials comparing immediate surgical intervention (<24 hours from time of admission) versus delayed therapy (>24 hours from time of admission).
- B. Retrospective reviews of studies comparing the outcomes of patients treated early in their disease versus those who had delayed therapy.
- C. Retrospective reviews of studies of patients with a diagnosis of necrotizing fasciitis from multiples etiologies.
- D. Prospective studies of patients with GAS necrotizing fasciitis.

Answer: C All of the reports of outcomes of necrotizing fasciitis have been studies that have included necrotizing fasciitis from multiple causes. There have been no prospective studies comparing immediate surgical intervention (<24 hours from time of admission) versus delayed therapy (>24 hours from time of admission). The published studies are all based on retrospective chart review of patients with necrotizing fasciitis from multiple etiologies, including mixed aerobic and anaerobic organisms.

4. Since the 1970s, group B streptococcus (GBS) is recognized as one of the most common causes of neonatal infectious morbidity and mortality in developed countries. Which of the following statements is correct?

- A. Although the transmission rate from mothers colonized with *S. agalactiae* to neonates delivered vaginally is approximately 50%, only 1% to 2% of colonized neonates go on to develop invasive GBS disease.
- B. Late GBS neonatal sepsis is defined as infection that presents between 1 week postpartum and age 3 months. Late disease commonly involves transmission of GBS from mother to baby after discharge.
- C. The current approach to the prevention of early-onset GBS infection in pregnancy requires prepartum antimicrobial prophylaxis in women in their last trimesters of pregnancy with culture evidence of recent vaginal or rectal GBS infection.
- D. Early-onset GBS disease can still occur in infants whose mothers screened negative for GBS colonization. Therefore, all women should receive intrapartum antibiotic prophylaxis regardless of screening results.

Answer: A The ability of the organism to cause invasive disease is related to the virulence and preexisting immunity from the mother. Virulence of *S. agalactiae* is related to the polysaccharide toxin it produces. Immunity is mediated by antibodies to the capsular polysaccharide and is serotype specific. Several serotypes are known, including Ia, Ib, Ic, II, III, IV, V, VI, VII, and VIII. A minority of infants with GBS late-onset disease are born to GBS-colonized mothers. Intrapartum prophylaxis does not appear to prevent late-onset GBS disease, implicating infected breast milk and nosocomial or community sources in these cases.

Multiple clinical trials have demonstrated that the use of intrapartum penicillin or ampicillin significantly reduces the rate of neonatal colonization with GBS and the incidence of early-onset neonatal GBS disease. Even in the setting of a maternal GBS screening program, efforts to evaluate and treat infants with intrapartum clinical risk factors for early-onset sepsis remain important. Results of studies have demonstrated that prompt intrapartum antibiotic treatment of women with signs and symptoms of chorioamnionitis regardless of their GBS screening results and the evaluation of well-appearing infants for possible sepsis because of intrapartum clinical risk factors remain imperative.

5. The *S. anginosus* group includes three distinct species and more subspecies. *S. anginosus*, *S. constellatus*, and *S. intermedius* have all been collectively known as *S. anginosus*. Characteristics of this group include

- A. Being part of the normal flora of the genitourinary tracts.
- B. The *S. anginosus* group should be considered true pathogens when isolated from humans.
- C. *S. milleri* is a closely related viridans group streptococci that is more frequently a cause of endocarditis.
- D. Lung infections caused by the *S. anginosus* group are largely confined to the right middle lobe.

Answer: B Although part of the normal flora, the group has the ability to cause abscesses and systemic infections, unlike *S. pyogenes* and *S. agalactiae*. The *S. anginosus* group is a heterogeneous group of organisms that can be human commensals, colonizing the gastrointestinal tract and the oral mucosa. The *S. anginosus* group is generally considered to be of low pathogenic potential in immunocompetent individuals. The *S. anginosus* group is one that has been the source of much controversy and confusion regarding taxonomy and classification. The group includes *S. anginosus*, *S. constellatus*, and *S. intermedius*. However, each of these species has been known as *S. anginosus* or *S. milleri* at one time. *S. milleri* has never been accepted as a confirmed taxonomic entity, although historically, it has been widely used interchangeably with the *S. anginosus* group. Thoracic infections caused by *S. anginosus* group are largely pleural. They are polymicrobial in one third of cases, and in most patients, are associated with major surgery or surgical procedures of the respiratory or digestive tract. The empyema frequently requires thoracotomy for complete resolution. In the chest, infections tend to cause loculated empyemas that are not conducive to tube thoracostomy drainage or to antibiotic treatment alone. About 75% of infections of the chest require surgical intervention.

Ch / 291 ENTEROCOCCAL INFECTIONS

1. Which of the following is a characteristic of the growth of Enterococci?

- A. The ability to grow in NaCl broth
- B. The β -hemolytic reaction on sheep blood agar
- C. The lack of growth on media containing bile
- D. The lack of esculin hydrolysis

Answer: A Enterococci are facultative anaerobes that grow optimally at 35°-37 °C and are usually β -hemolytic or nonhemolytic on sheep blood agar. Enterococci can grow in broth containing 6.5% NaCl and hydrolyze esculin in the presence of 40% bile salts (bile-esculin medium) which can distinguish them from most streptococci.

2. Vancomycin-resistant enterococci (VRE) are the result of

- A. the acquisition of VanA gene from VRSA (vancomycin-resistant *Staphylococcus aureus*).
- B. the selective pressure of antimicrobials on enterococci, including vancomycin.
- C. an efflux pump highly active on vancomycin.
- D. a porin loss limiting the vancomycin action on the cell wall

Answer: B An example of selective pressure was demonstrated in Europe when the use of specific antimicrobials in animals led to the development of resistance.

3. Among the following antimicrobials, which one is not a treatment of enterococci?

- A. Daptomycin
- B. Ampicillin
- C. Vancomycin
- D. Clindamycin

Answer: D (See section on Treatment.)

4. Enterococci are commonly associated with all of these clinical manifestations except

- A. wound infection.
- B. urinary tract infection.
- C. bacteremia.
- D. osteomyelitis.

Answer: D Enterococci are known to cause urinary tract infections, intra-abdominal abscesses, wound infections, bacteremia, including catheter-associated bloodstream infections, and endocarditis; less commonly, they cause osteoarticular infections and meningitis.

5. All of the answers below are needed to control the transmission of VRE among hospitalized patients except

- A. hand hygiene.
- B. contact precaution.
- C. screening and treatment of colonized patients with effective antimicrobials.
- D. antimicrobial stewardship programs.

Answer: C Screening or surveillance is important to identify the colonized patient and to assure isolation in contact precautions but treatment of colonization is not recommended. Limiting antimicrobial use will help decrease the selective pressure.

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DIPHTHERIA AND OTHER *CORYNEBACTERIUM* INFECTIONS

1. A 61-year-old Vietnam veteran with a low socioeconomic status (SES) in Seattle is brought to the emergency department (ED) because of difficulties breathing. On radiography, a lobar pneumonia is demonstrated, and appropriate treatment with antibiotics is initiated. The attending ED physician also notes a rash on the lower extremity. The lesions are deep punched-out non-itching ulcers that are indolent. On culture, *Staphylococcus aureus* is grown. What is the likely diagnosis of the skin rash?

- A. Impetigo
- B. Cutaneous diphtheria
- C. Chronic dermatitis superinfected by *S. aureus*
- D. Cat scratch disease
- E. Scabies.

Answer: B Cutaneous lesions caused by *Corynebacterium diphtheriae* are typically deep punched-out ulcers in a patient at risk (low SES, probably alcohol abuse, poor hygiene). The isolation *S. aureus* (or other skin bacteria) occurs frequently. *C. diphtheriae* may not be cultured initially because of the need for special media. Impetigo and chronic dermatitis are possible diagnoses but are unlikely given the typical appearance of the lesions (usually honey-colored scabs). Similarly, cat scratch disease is unlikely in the absence of a supporting history of contact with cats. Scabies causes a papular rash with intense itching.

2. A 23-year-old Peace Corps volunteer returns from a 2-year assignment in the rural East Java Province of Indonesia. She presents with sore throat, malaise, and mild to moderate fever for 3 days. Before leaving Indonesia, the patient received erythromycin. On examination, a whitish membrane adheres tightly to the right tonsil. During the swabbing of the tonsil for culture, the membrane cannot be removed and starts to bleed at the edge. What is the most likely diagnosis?

- A. Streptococcal tonsillitis
- B. Plaut-Vincent angina
- C. Respiratory diphtheria
- D. Primary syphilis lesion
- E. Infectious mononucleosis (MN) caused by Epstein-Barr virus (EBV)

Answer: C A greyish white pseudomembrane on a tonsil should lead to a high suspicion for diphtheria, as does the history of an extended stay in a developing country where diphtheria is endemic. None of the other diagnoses are associated with the formation of a pseudomembrane.

3. Given a high index of suspicion of respiratory diphtheria in this 23-year-old patient (see question 2), what is the immediate priority?

- A. Report the suspected case to the local health department.
- B. Inform the laboratory to use special media for culturing (potassium tellurite media).
- C. Contact the Centers for Disease Control and Prevention and order equine diphtheria antitoxin.
- D. Check the patient's diphtheria toxoid vaccination history.
- E. Isolate the patient.

Answer: E In order of priority, it is essential to ensure that the airways are patent. In this case, we have no indication that these are compromised. After the diagnosis of suspected diphtheria is established, the patient needs to be isolated to prevent spread to contacts. The isolation of *Corynebacterium diphtheriae* requires a special media, so the laboratory has to be alerted. Given that the patient has been taking antibiotics for several days, it is unlikely the culture result will be positive. However, because of the potential complications of diphtheria, treatment with equine diphtheria antitoxin should be initiated on the basis of suspicion as soon as possible. Then the local health department should be contacted.

4. Which one is not a likely complication of diphtheria toxin?

- A. Myocarditis
- B. Kidney (tubular necrosis)
- C. Neuropathy (caused by demyelination)
- D. Encephalitis
- E. Respiratory insufficiency

Answer: D Encephalitis is not a likely complication of diphtheria. Myocarditis occurs up to several weeks after the onset of acute respiratory diphtheria and is associated with a high fatality rate. The kidneys may be affected but recover. The most common form of neuropathy is palatal paralysis or peripheral neuropathy in the lower extremity; both are reversible. Extension of diphtheric membranes into the respiratory tree can lead to respiratory stress and even insufficiency.

5. What recommendations for diphtheria antitoxin vaccination would you make to a 26-year-old oil worker going to the Middle East for several months? The man had received two doses of diphtheria, tetanus, and pertussis (Tdap) vaccine as a child and is leaving the United States in 6 weeks.

- A. Give a dose of diphtheria toxoid-containing vaccine (d).
- B. Administer a dose of tetanus and diphtheria toxoid (Td).
- C. Complete the vaccination schedule with adult-formulation Tdap vaccine before departure.
- D. Given the possible adverse events and the unlikely exposure to diphtheria in the oil fields, no further immunization is recommended.
- E. Complete the schedule with infant-formulation Tdap vaccine before departure.

Answer: C To have protective antitoxin levels, a full primary series of diphtheria toxin-containing vaccine is needed. In this instance, administer a dose now and a second dose 4 weeks later. A single dose of diphtheria toxoid would be suboptimal and would be a missed opportunity for vaccinating against tetanus and pertussis.

6. Which of the following statements about diphtheria immunization is correct?

- A. DTP (diphtheria and tetanus toxoid and pertussis vaccine) should not be administered to pregnant women because of the risk of adverse pregnancy outcomes.
- B. Diphtheria-specific IgG levels are higher in infants when their mothers were immunized with DTP 2 years before delivery than when their mothers received DTP in midpregnancy.
- C. Adults require boosters of diphtheria toxoid every 10 years even after completing a full series of infant immunizations plus preschool and adolescent boosters.
- D. A single booster administration in an adult who had never received DTP immunizations in childhood will provide adequate protection.

Answer: D For adults older than 19 years of age who have never received a dose of DTP, the U.S.

Centers for Disease Control and Prevention still recommends the routine use of a single dose of DTP to replace the next booster dose. The Vaccine Adverse Event Reporting System has not identified any concerning events in maternal, infant, or fetal outcomes in pregnant women who received DTP. It has been demonstrated that protective IgG levels in the infants of women immunized with DTP within the past 2 years before delivery is the same as those in infants whose mothers were immunized in the second or third trimester. In fact, it is now suggested that vaccinating mothers in the late second or third trimester of pregnancy is safe and would more likely allow maternal antibody production to reach higher protective levels (to be transferred across the placenta to the fetus) by the time of delivery. The diphtheria prevention protocol involves a primary series of 4 doses of diphtheria toxoid (in the form of DPT) to be administered at 2, 4, 6, and 15 to 18 months; a preschool booster dose to be given at 4 to 6 years of age, and subsequent boosters to be given as part of adolescent immunization visits (between 11 and 13 years of age) followed thereafter by doses administered every 10 years. (See section on Prevention and Kao CM, Schneyer RJ, Bocchini JA. Child and adolescent immunizations: selected review of recent US recommendations and literature. *Office Pediatr.* 2014;26:383-395.)

7. Which of the following statements about diphtheria is correct?

- A. Outbreaks of diphtheria can be caused either by clonal spread of toxigenic strains or by transfer of the gene for the toxin via bacteriophage to nontoxigenic strains.
- B. The case-fatality rate for diphtheria has decreased dramatically since the advent of childhood immunization for the disease.
- C. The extent of diphtheria toxin absorption into the circulation is not dependent on the primary site of infection.
- D. Nontoxigenic strains of *Corynebacterium diphtheriae* do not cause clinical illness in humans.
- E. Cutaneous diphtheria in North America and Europe occurs almost exclusively in severely immunocompromised individuals.

Answer: A Outbreaks of serious illness can be caused by either toxigenic strains or nontoxigenic strains that have been made toxigenic by transfer of the toxin gene by phages. Infection by nontoxigenic strains of *C. diphtheriae* can cause symptoms, although typically much milder than those caused by toxigenic strains. Although the incidence of diphtheria has plummeted throughout most of the world since the advent of childhood immunization, the case-fatality rate has not changed much; it remains a very serious disease (with case-fatality of 5% to 10% in the United States). The extent of toxin absorption varies with the site of infection, being much less from the skin or nose than from the pharynx. Outbreaks of cutaneous diphtheria have occurred in the United States and Europe typically in homeless and alcoholic inner-city adults, not necessarily those who are severely immunocompromised.

1. Which one of the following individuals is at the highest risk for invasive listeriosis?

- A. A 25-year-old with common variable hypogammaglobulinemia
- B. A 45-year-old being treated with an anti-tumor necrosis factor agent
- C. A 38-year-old with a splenectomy
- D. A 52-year-old who has had leukemia and neutropenia
- E. A 72-year-old on hemodialysis

Answer: B Invasive listeriosis occurs most often in those with impaired cell-mediated immunity due to underlying disease or due to treatment with drugs such as corticosteroids or anti-tumor necrosis factor agents. Splenectomy, disorders of white blood cell numbers or function, and immunoglobulin disorders are not associated with an increased risk.

2. A 66-year-old man presents with fever and altered consciousness. The findings on examination of his cerebrospinal fluid (CSF) are consistent with bacterial meningitis, and CSF Gram stain shows small, gram-positive rods. He had an anaphylactic reaction to amoxicillin 2 years ago. Which one of the following is the best treatment for this patient?

- A. Ceftriaxone
- B. Vancomycin
- C. Imipenem
- D. Trimethoprim-sulfamethoxazole
- E. Aztreonam

Answer: D Gram-positive rods in the CSF of a patient with meningitis most likely represent *Listeria monocytogenes*. In those with severe penicillin allergy, trimethoprim-sulfamethoxazole is the recommended agent to treat listerial meningitis. No cephalosporin should be used to treat listeriosis. Vancomycin and imipenem are active in vitro, but treatment failures have been reported. Aztreonam has no anti-listerial activity.

3. An elderly woman is hospitalized with meningitis due to *Listeria monocytogenes*. Which one of the following types of isolation is appropriate for this patient?

- A. No isolation required
- B. Contact isolation
- C. Airborne isolation
- D. Droplet isolation

Answer: A Except for transmission from mother to fetus or newborn, human-to-human transmission of listeriosis has not occurred. No isolation is required for those infected with *L. monocytogenes*.

4. Which one of the following is the mechanism by which *Listeria monocytogenes* avoids being killed by phagocytic cells?

- A. Inhibition of chemotaxis
- B. Inhibition of attachment
- C. Inhibition of ingestion
- D. Suppression of the metabolic burst
- E. Escape from the phagosome

Answer: E The exotoxin, listeriolysin O, is the major virulence factor of *L. monocytogenes* and enables the bacterium to escape from the phagocytic vacuole, whereupon it multiplies in the phagocytic cell cytoplasm.

5. An elderly man is found to have a brain abscess. Which one of the following features is strongly suggestive of *Listeria monocytogenes* as the abscess etiology rather than a more common pathogen?
- A. Absence of fever
 - B. Absence of leukocytosis
 - C. Location in the pons
 - D. Focal neurologic findings
 - E. Presence of seizures

Answer: C Unlike the usual causes of brain abscess, *Listeria* has a particular tropism for the brain stem. Subcortical brain abscesses due to other pathogens are rare; the presence of a subcortical brain abscess should always raise the possibility of listerial infection.

Ch / 294 **ANTHRAX**

1. A 56-year-old man is diagnosed with inhalational anthrax. His blood cultures are positive for *Bacillus anthracis*. His noncontrast chest computed tomography scan shows mediastinal adenopathy and moderate-sized bilateral pleural effusions. He is receiving several appropriate antibiotics. According to the 2014 anthrax management guidelines from the Centers for Disease Control and Prevention (CDC), what is recommended to be done with regard to the pleural effusions?
- A. Follow closely on a daily basis to be sure they decrease in size with antibiotics.
 - B. Drain by thoracentesis only if they enlarge after 48 hours with antibiotics.
 - C. Drain immediately by thoracentesis but without chest tube drainage.
 - D. Perform thoracentesis on one side and send fluid for anthrax toxin levels.
 - E. Perform bilateral chest tube drainage at this time.

Answer: E Retrospective analysis of the 1979 inhalational anthrax outbreak in Sverdlovsk, USSR, the 2001 outbreak in the United States, and the recent findings of high levels of anthrax toxin in the pleural fluid support the CDC's 2014 guidelines on aggressive management of pleural effusions. The CDC now advises: "Drainage of pleural fluid and ascites is believed to improve survival by reducing the toxin level and by decreasing mechanical lung compression. These data support the need for early and aggressive drainage of any clinically or radiographically apparent pleural effusions; chest tube drainage is recommended over thoracentesis because many effusions will require prolonged drainage."

2. In December 2012, the Food and Drug Administration (FDA) licensed the first anthrax antitoxin. This product is a humanized monoclonal antibody. Which of the following choices is *not* included in the FDA licensure of this antitoxin?
- A. Treatment of children during any stage of inhalational anthrax
 - B. Treatment of adults during any stage of inhalational anthrax
 - C. Treatment of children with only early-stage inhalational anthrax
 - D. Postexposure prophylaxis when alternative therapies are unavailable
 - E. Postexposure prophylaxis when alternative therapies are not appropriate.

Answer: C This monoclonal anthrax antitoxin was licensed by the FDA in December 2012 for treatment of inhalational anthrax in both children and adults at any stage of the disease (early prodromal, intermediate progressive, or late fulminant). In addition, this antitoxin was licensed for postexposure prophylaxis in both children and adults "when alternative therapies are not available or not appropriate." (See discussion in the Prevention and Treatment sections.)

3. The CDC recommendations for use of the anthrax vaccine specifically for postexposure prophylaxis, in addition to an antibiotic, is for which of the following number of vaccine doses and schedules?
- A. One dose of vaccine as soon as possible after exposure to spores
 - B. Two doses of vaccine during a 1-month period
 - C. Three doses of vaccine during a 1-month period
 - D. Three doses of vaccine during a 12-month period
 - E. Five doses of vaccines during an 18-month period

Answer: C Anthrax vaccine is recommended by the CDC in their 2014 guidelines specifically for postexposure prophylaxis as three doses of vaccine given during a 1-month period. In contrast, the FDA-licensed anthrax vaccine for the traditional preexposure use requires five injections given during an 18-month period. (See discussion in the Prevention section.)

4. Antibiotics that are approved by the FDA for postexposure prophylaxis include all of the following except
- A. Levofloxacin
 - B. Ciprofloxacin
 - C. Procaine penicillin G
 - D. Clindamycin
 - E. Doxycycline

Answer: D Ciprofloxacin, doxycycline, levofloxacin, and procaine penicillin G are all approved by the FDA for postexposure prophylaxis use to prevent symptomatic anthrax. Clindamycin is not approved for postexposure prophylaxis; however, it is included in the 2014 CDC recommendations for treatment of some patients with symptomatic anthrax infection. (See discussion in the Prevention section.)

5. Blood culture samples drawn before antibiotics are administered typically will start growing *Bacillus anthracis* in patients with inhalational anthrax within what time frame?
- A. 6 hours
 - B. 24 hours
 - C. 48 hours
 - D. 1 week
 - E. Will not grow in standard culture media

Answer: B A striking and consistent finding in all patients since the 2001 U.S. outbreak of inhalational anthrax is the growth within 24 hours of *Bacillus anthracis* from blood cultures of patients who were not already receiving antibiotics when the blood culture samples were drawn. This crucial observation emphasizes the diagnostic importance of drawing blood culture samples in any patient suspected of having inhalational anthrax before antibiotics are started. (See discussion in the Diagnosis section.)

1. A 56-year-old fisherman, who has no significant medical problems, presents with a 2-week history of a well-defined, elevated, painful, reddish purple plaque on the dorsum of his right hand. The lesion has been slowly expanding during the course of 2 weeks and appeared approximately 1 week after his last fishing trip. He is afebrile, and there is no evidence of regional lymphadenopathy or lymphadenitis. Which of the following is the most appropriate recommendation?

- A. Aspirate the leading edge and send any material for Gram stain and culture.
- B. Begin oral penicillin.
- C. Refer for a biopsy of the lesion.
- D. Begin intravenous vancomycin.
- E. No treatment

Answer: B This patient has classic erysipeloid, caused by *Erysipelothrix rhusiopathiae*. It is a zoonosis that is linked to certain occupations, including fishermen. The lesion is a cellulitis that is generally found on the hands or fingers, and the organism is introduced through cuts and abrasions of the skin. Systemic signs of infection are rare. Although uncomplicated skin lesions may resolve spontaneously during a period of 3 weeks, a short course of oral penicillin G hastens healing and is the treatment of choice. The organism is resistant to vancomycin. Because the organism is located in deeper parts of the skin and there is not any suppuration, in cases of erysipeloid, aspiration is unlikely to lead to recovery of the organism. A biopsy of the entire thickness of the dermis at the edge of the lesion would yield maximum recovery of the organism but is not indicated because of the classic presentation and the ease of treatment with penicillin. (Veraldi S, Girgenti V, Dassoni F, et al. Erysipeloid: a review. *Clin Exp Dermatol*. 2009;34:859-862.)

2. A 47-year-old man with a history of chronic liver disease, secondary to alcohol use, presents with a 3-day history of fever, chills, and generalized arthralgias. He works in a slaughterhouse that processes pigs. Approximately 3 weeks ago, he developed a cellulitis of his finger that resolved spontaneously without therapy. Blood culture samples are obtained and yield gram-positive bacilli that are identified as *Erysipelothrix rhusiopathiae*. An echocardiogram is normal, and follow-up blood cultures are negative. The antibiotic therapy of choice is

- A. Vancomycin
- B. Intravenous penicillin G
- C. Tetracycline
- D. Ampicillin and gentamicin
- E. Trimethoprim-sulfamethoxazole

Answer: B This patient has bacteremia without infective endocarditis. *Erysipelothrix rhusiopathiae* bacteremia without endocarditis occurs more frequently than was previously believed and is occurring with increased frequency in immunocompromised patients, including those with liver disease. The treatment of choice for systemic infections is intravenous penicillin G. *E. rhusiopathiae* is resistant to vancomycin, aminoglycosides, tetracycline, and trimethoprim-sulfamethoxazole. (Wang Q, Chang BJ, Riley TV. *Erysipelothrix rhusiopathiae*. *Vet Microbiol*. 2010;140:405-417.)

3. A 45-year-old veterinarian presents with a 2-week history of fever, chills, and sweats. On physical examination, he is noted to have a 3/6 diastolic murmur, consistent with aortic regurgitation. Three sets of blood cultures are positive for *Erysipelothrix rhusiopathiae*, and an echocardiogram reveals a vegetation on the aortic valve. He has an allergy to penicillin, which is manifested as hives. The most appropriate alternative antibiotic therapy is

- A. Vancomycin
- B. Ceftriaxone
- C. Daptomycin
- D. Ampicillin and gentamicin
- E. Tetracycline

Answer: C This patient has infective endocarditis of the aortic valve caused by *Erysipelothrix rhusiopathiae*. *E. rhusiopathiae* endocarditis correlates highly with occupation, exhibits a tropism for the aortic valve, and affects more males than females. Penicillin is the treatment of choice; daptomycin and quinolones are alternative therapies when the patient is allergic to β -lactams. For a patient with an immediate hypersensitivity reaction to penicillin, cephalosporins are contraindicated because of possible cross-reactivity. *E. rhusiopathiae* is resistant to vancomycin, tetracyclines, aminoglycosides, and trimethoprim-sulfamethoxazole. Even if there was not a concern for resistance, tetracyclines are bacteriostatic, and it is necessary to administer bactericidal agents for the treatment of endocarditis. (Piper KE, Steckelberg JM, Patel R. In vitro activity of daptomycin against clinical isolates of gram-positive bacteria. *J Infect Chemother*. 2005;11:207-209.)

4. A 60-year-old man with a history of rheumatoid arthritis, who is being treated with prednisone chronically, presents to his physician to discuss prevention of infection with *Erysipelothrix rhusiopathiae*. He has a friend who works in the slaughterhouse with him who recently was treated for endocarditis caused by *E. rhusiopathiae*. The physician should recommend the following:

- A. Vaccination
- B. Chronic low-dose therapy with oral penicillin while he is receiving prednisone
- C. Good hand hygiene and use of protective gloves
- D. Use of a gown, mask, and gloves while at work

Answer: C *Erysipelothrix rhusiopathiae* is an occupational pathogen that is transmitted through traumatic contact with infected animals or animal products. Occupations at risk include fishermen, farmers, veterinarians, and slaughterhouse workers. Immunocompromised hosts are at risk for infection. The transmission of *Erysipelothrix* generally occurs by traumatic inoculation through abrasions or cuts in the skin of the hands and rarely through consumption of contaminated meat or fish products. Proper cleaning and disinfection of work surfaces and attention to hygienic work practices, including good hand hygiene and the use of gloves, reduce the risk of infection. Vaccines are available for commercial use in animals only, and there are currently no known vaccines that are available for humans. There is no documentation of transmission by droplets or aerosols, and therefore masks are not indicated. (Wang Q, Chang BJ, Riley TV. *Erysipelothrix rhusiopathiae*. *Vet Microbiol*. 2010;140:405-417.)

5. A 63-year-old woman with a history of chronic eczema and alcoholism underwent a right knee arthroplasty for degenerative joint disease. She lived on a farm that raised swine. Six months after the arthroplasty, she developed pain and swelling of the right knee, with subsequent drainage of purulent material from a pustule in the incision. Plain radiographs revealed loosening of the prosthesis and osteomyelitis. She underwent removal of the prosthesis, and multiple operative samples of fluid and bone revealed gram-positive rods. Cultures were positive for *Erysipelothrix rhusiopathiae*. Blood cultures were negative. She was treated with intravenous imipenem for 2 weeks. Which of the following is the most appropriate recommendation for outpatient oral therapy?

- A. Clarithromycin
- B. Tetracycline
- C. Trimethoprim-sulfamethoxazole
- D. Ciprofloxacin

Answer: D Most isolates of *Erysipelothrix rhusiopathiae* are susceptible to penicillin, cephalosporins, imipenem, clindamycin, ciprofloxacin, ofloxacin, and daptomycin. Resistance has been observed with erythromycins, tetracyclines, and chloramphenicol. *E. rhusiopathiae* is also resistant to vancomycin, aminoglycosides, trimethoprim-sulfamethoxazole, and sulfonamides. An oral fluocinolone, such as ciprofloxacin, has excellent efficacy in the treatment of osteomyelitis and septic arthritis. Although arthritis is one of the most common features of *E. rhusiopathiae* infection in animals, this type of infection is relatively rare in humans. There are about 12 cases of bone and joint infection reported in the medical literature. Most patients had a skin lesion at the site of the infected joint and have an occupational or recreational exposure to an animal reservoir of infection. (Hocqueloux L, Poisson DM, Sunder S, et al. Septic arthritis caused by *Erysipelothrix rhusiopathiae* in a prosthetic knee joint. *J Clin Microbiol*. 2010;48:333-335.)

1. What is the preferred treatment for a patient with a first episode of mild to moderate *C. difficile* infection (CDI)?

- A. Metronidazole 500 mg orally three times a day for 10 days
- B. Vancomycin 125 mg orally four times a day for 10 days
- C. Fidaxomicin 200 mg orally twice a day for 10 days
- D. Fecal microbiota transplant
- E. A or B

Answer: E This is an evolving area of treatment recommendation that will likely change with update of the CDI guidelines, so E is the current best answer. Both metronidazole and vancomycin orally are effective for mild to moderate CDI treatment, but the publication of the largest randomized controlled trial of metronidazole versus vancomycin demonstrated that metronidazole was significantly inferior to vancomycin ($P = .02$) for all patients with CDI, which is likely to change future recommendations to vancomycin. A1 Fidaxomicin is also effective but is much more expensive than metronidazole or vancomycin. A2, A3 Fecal transplants are also effective, but experience with them has been limited to treatment of patients with multiple recurrences of CDI, for which it is effective in preventing additional recurrences. A4

2. What is the preferred treatment for patients with severe first-episode CDI?

- A. Metronidazole 500 mg orally three times a day for 10 days
- B. Vancomycin 125 mg orally four times a day for 10 days
- C. Fidaxomicin 200 mg orally twice a day for 10 days
- D. Both A and B used together
- E. Metronidazole 500 mg IV three times a day plus vancomycin 500 mg orally four times a day for 10 days

Answer: B CDI guidelines recommend vancomycin for severe CDI.³ Metronidazole was inferior to vancomycin for severe CDI in one randomized controlled trial and was inferior to vancomycin for all CDI in another larger randomized controlled trial. A1 Fidaxomicin is also effective in treating severe CDI, but it is no better than vancomycin in eliciting cure; however, it is superior in reducing recurrence of CDI. Because of much higher pricing than for vancomycin, it is not the preferred treatment of first-episode CDI. Combined use of metronidazole and vancomycin has not been demonstrated to be superior to vancomycin alone for severe disease; however, use of IV metronidazole and higher dose oral vancomycin is recommended for severe complicated or fulminant CDI where there is significant risk of ileus that might prevent oral vancomycin from reaching the colon.

3. A California injection heroin user is “skin popping” because of exhausting all intravenous sites of injection. He has noted increased swelling and pain at an arm injection site during the past week and now also notes that his vision is blurred and his speech is slurred, and he has chills and feels weak and feverish. The most likely cause of his symptoms is

- A. *Clostridium novyi* injection site abscess
- B. *Clostridium tetani* injection site infection
- C. *Clostridium botulinum* infection at the injection site
- D. *Clostridium perfringens* injection site abscess
- E. *Clostridium sordelli* injection site infection

Answer: C Most drug injection site infections are polymicrobial, and any of the listed clostridia could be present in addition to other anaerobes and aerobic bacteria, such as staphylococci and streptococci. However, of the clostridia listed, only *C. botulinum*, the cause of botulism, is associated with the symptoms of blurred vision, slurred speech, and weakness, a hallmark of early cranial nerve involvement and descending paralysis.

4. Which of the following statements about tetanus is *not* true?

- A. It is the cause of hundreds of thousands of neonatal deaths globally because of inadequate maternal tetanus vaccination.
- B. Although it is rare in the United States, most cases occur in patients inadequately vaccinated.
- C. A short incubation period from injury to tetanus symptoms is indicative of a rapid resolution of symptoms and increased survival.
- D. Immunization of childbearing women with Tdap (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis) is recommended during the third trimester of each pregnancy for optimal fetal passive antibody protection, which is largely directed at preventing pertussis.
- E. The mortality rate for generalized tetanus is 20 to 25%, even in modern medical facilities with extensive resources.

Answer: C This statement is incorrect. The shorter the period from injury to tetanus symptoms, the worse the prognosis is and the longer symptoms are likely to last. The other statements are all true.

5. Which clostridial organism is most likely responsible for the following syndrome? A 12-year-old boy with poorly controlled type 1 diabetes mellitus was admitted to the hospital with ketoacidosis and altered mental status 2 to 3 days after eating several large meals that included chitterlings. His white blood cell count was 11,300 mm³, and his abdominal radiograph showed dilated loops of small bowel with gas in the bowel wall. His hospital course was notable for persistent hematemesis and increasing abdominal distention. Bloody ascites and necrotic jejunum and ileum were found at laparotomy.

- A. *C. difficile*
- B. *C. perfringens* type A
- C. *C. perfringens* type C
- D. *C. sordellii*
- E. *C. botulinum*

Answer: C Although it is rare in developed countries, enteritis necroticans due to *C. perfringens* type C is responsible for this unique syndrome of small intestinal necrosis. Diabetes mellitus is a common risk factor noted in cases outside endemic areas, as in this case, which was reported in the southern United States in 2000. (Petrillo TM, Beck-Sagué CM, Songer JG, et al. Enteritis necroticans [pigbel] in a diabetic child. *N Engl J Med*. 2000;342:1250-1253.) *C. difficile* may cause severe intestinal disease, but disease is limited to the colon. *C. perfringens* type A rarely causes necrotizing intestinal syndromes, but again, disease is typically limited to the colon. *C. sordellii* and *C. botulinum* are usually not associated with acute abdominal syndromes.

1. What culture is appropriate for isolation of anaerobic bacteria?

- A. Vaginal or cervical swabs
- B. Routine or catheterized urine
- C. Throat or nasopharyngeal swabs
- D. Aspirate of abscess
- E. Feces or rectal swabs

Answer: D Obtaining an aspirate after sterilizing the skin or bypassing the normal flora avoids contamination of the specimen by normal skin or mucous membrane bacterial flora.

2. *Bacteroides fragilis* bacteremia is usually associated with

- A. Trauma
- B. Aspiration
- C. Rupture of abdominal viscus
- D. Malignant disease
- E. Osteomyelitis

Answer: C Although *B. fragilis* group is the most common species found in clinical specimens, it is the least common *Bacteroides* present in fecal flora, representing only 0.5% of the bacteria present in stool. The pathogenicity of this group of organisms probably results from its ability to produce capsular material, which is protective against phagocytosis. Because of its presence in normal flora of the gastrointestinal tract, this organism is predominant in bacteremia associated with intra-abdominal infections, peritonitis, and abscesses following rupture of a viscus.

3. Which of the following antimicrobials is not effective against anaerobic bacteria?

- A. Amoxicillin
- B. Metronidazole
- C. Gentamicin
- D. Moxifloxacin
- E. Cefoxitin

Answer: C Aminoglycosides, including gentamicin, are not effective against anaerobic bacteria because of their inability to reach the ribosome. Gentamicin is effective only in aerobic microorganisms because it enters cells through an electron transport-linked system that requires oxygen.

4. Which anaerobic organism cannot produce β -lactamase?

- A. *Fusobacterium nucleatum*
- B. *Bacteroides fragilis*
- C. *Prevotella melaninogenica*
- D. *Peptostreptococcus* spp
- E. *Bacteroides thetaiotaomicron*

Answer: D Most *B. fragilis* group, up to 20 to 50% of *Prevotella* spp, and *Fusobacterium nucleatum* isolates can produce β -lactamase.

5. *Propionibacterium acnes* is associated with

- A. Chronic sinusitis
- B. Splenic abscess
- C. Cellulitis
- D. Abdominal trauma
- E. Central nervous system shunt infection

Answer: E *Propionibacterium* species are part of the normal bacterial flora that colonizes the skin, conjunctiva, oropharynx, and gastrointestinal tract. These non-spore-forming, anaerobic, gram-positive bacilli are frequent contaminants of specimens of blood and other sterile body fluids and have been generally considered to play little or no pathogenic role in humans. *Propionibacterium acnes* has, however, been recovered in specimens obtained from patients with infections associated with a foreign body (such as an artificial valve), endocarditis, and central nervous system shunt infections.

1. *Neisseria meningitidis* is a

- A. Gram-negative rod causing pneumonia and bacteremia
- B. Gram-positive diplococcus causing primarily pneumonia
- C. Gram-negative diplococcus causing epidemic meningitis and septicemia
- D. Gram-positive rod causing meningitis in immunocompetent patients
- E. Gram-variable coccobacillus causing meningitis and otitis media

Answer: C *N. meningitidis* is an aerobic, diplococcal gram-negative β -proteobacterium and a member of the family Neisseriaceae, which also includes *Neisseria gonorrhoeae* (Chapter 299), another important human pathogen. *N. meningitidis* is the cause of epidemic bacterial meningitis, fulminant sepsis (meningococemia), milder bacteremia, and, less commonly, focal infections (such as pneumonia, septic arthritis, purulent pericarditis, and conjunctivitis).

2. Serogroup A *N. meningitidis*

- A. Causes significant disease in the United States and Japan
- B. Has been a major cause of epidemic meningococcal outbreaks in sub-Saharan Africa
- C. Expresses a sialic acid capsule
- D. Has no effective vaccine
- E. Is usually treated with sulfonamides

Answer: B In sub-Saharan Africa, seasonal increases in disease and cyclic pandemics, which have occurred every 8 to 10 years since 1905, have been predominantly caused by serogroup A *N. meningitidis*. A new serogroup A conjugate vaccine introduced in 2010 has rapidly lowered the incidence of meningococcal disease in this region.

3. Which one is not true? The rash of invasive meningococcal disease

- A. Can be a blanching macular rash
- B. Is typically petechial or purpuric
- C. Can be confused with leukocytoclastic vasculitis, Rocky Mountain spotted fever, and enteroviral infections
- D. Is almost always present and easily detected
- E. Is usually a single "bull's-eye" lesion

Answer: D Hemorrhagic skin lesions (petechiae, purpura; Fig. 298-3) are present in 28 to 77% of patients with invasive meningococcal disease on admission, but these lesions may be absent or difficult to see in patients with dark skin. A nonblanching macular rash can also be a manifestation of meningococcal bacteremia.

4. Which one is not true regarding antibiotic treatment of meningococcal meningitis?

- A. It should be administered as soon as the diagnosis is considered.
- B. It takes 10 to 14 days to be effective.
- C. Options include ceftriaxone or cefotaxime, penicillin, or meropenem.
- D. Quinolone resistance has been reported.
- E. Sulfonamide resistance is now common.

Answer: B Meningococci in cerebrospinal fluid are killed within 3 to 4 hours after intravenous treatment with an adequate dose of a third-generation cephalosporin or penicillin. Traditionally, patients with meningococcal meningitis were treated for 7 days or longer, but 3 or 4 days of intravenous treatment can provide a cure without relapse.

5. Which one is not true regarding prevention of meningococcal disease?

- A. Chemoprophylaxis is given to prevent secondary cases that occur usually 10 to 14 days after the primary case.
- B. Meningococcal polysaccharide- protein conjugate vaccines are a long-term control measure of meningococcal disease.
- C. Meningococcal vaccines have effectiveness in complement-deficient patients.
- D. Rifampin, ceftriaxone, ciprofloxacin, and azithromycin are used for chemoprophylaxis.
- E. Meningococcal polysaccharide vaccines are now preferred for prevention strategies.

Answer: E Meningococcal conjugate vaccines are safe and immunogenic in young children, induce immunologic memory, and can decrease nasopharyngeal carriage of meningococci. Meningococcal conjugate vaccines have largely replaced the older polysaccharide vaccines and are now preferred for prevention strategies.

Ch / 299 **NEISSERIA GONORRHOEAE INFECTIONS**

1. A 26-year-old man comes to your office complaining of pain with urination and a discharge from his penis. He reports having both insertive and receptive anal sex with two men in the last 2 months but says that he always uses condoms when having anal sex. He also reports both giving and receiving oral sex. The patient reports testing negative for HIV infection approximately 6 months ago. He thinks he had chlamydia several years ago but otherwise denies any prior history of sexually transmitted infection. Physical examination is notable for purulent urethral discharge. Your office does not have a microscope to allow you to perform a Gram stain. Which of the following would be part of the recommended management of this patient?

- A. Ceftriaxone 250 mg IM plus azithromycin 1 g PO as a single dose
- B. Test for HIV infection and syphilis.
- C. Test for gonorrhea (rectal, pharyngeal, and urethral gonorrhea) and chlamydial infection (urethral, rectal).
- D. Notify the health department of the patient's infection if he has laboratory confirmation of infection.
- E. All of the above

Answer: E This patient presents with typical signs and symptoms of urethritis. Although a urethral Gram stain would be useful in determining whether this patient has gonorrhea, most clinicians in the United States cannot perform Gram stains in their office, and the patient should be empirically treated for both gonorrhea and chlamydial infection. Ceftriaxone is more active against *Neisseria gonorrhoeae* than are third-generation oral cephalosporins like cefixime and should be used in this patient. The addition of azithromycin is designed both to treat a possible concurrent chlamydial infection and as a strategy to diminish the risk of selecting for antimicrobial resistance. Of note, this patient denies having unprotected anal sex, and his only clear urethral exposure is through oral sex. Although his history may be inaccurate, an ill-defined but probably sizable proportion of all urethral gonorrhea in men who have sex with men (MSM) is likely to be acquired through oral sex, highlighting the importance of screening for pharyngeal gonorrhea among MSM. In contrast, *Chlamydia trachomatis* infrequently infects the pharynx and probably is rarely transmitted by fellatio, and no readily available tests are approved for pharyngeal chlamydial infection.

2. A 19-year-old woman comes to your office requesting contraception. She recently started a new relationship with a man and sometimes uses condoms. Before her current sex partner, she reports not having sex for about 6 months. As part of her care, you perform a routine screening test for gonorrhea and chlamydial infection on a self-obtained vaginal swab using Aptima Combo 2, a nucleic acid amplification test. The test result comes back positive for both gonorrhea and chlamydial infection.

You call the patient to give her the results and arrange her follow-up. She continues to be asymptomatic. Which of the following would be part of your initial management of this patient?

- A. Have the patient return to your office for treatment with ceftriaxone 250 mg IM plus azithromycin 1 g PO as a single dose.
- B. Arrange for the patient to return to your office for follow-up testing in 3 months.
- C. Ask the patient to bring her partner to your office with her so that he can be treated.
- D. Talk to the patient and her partner about condoms and risk reduction when she returns to see you, and advise them to abstain from sex for 1 week after the completion of both of their treatment.
- E. All of the above

Answer: E A regimen of ceftriaxone and azithromycin is effective for both gonorrhea and chlamydial infection. Although a test of cure is not indicated among nonpregnant women with gonorrhea or chlamydial infection, repeated testing 3 months after treatment is recommended because of the high prevalence (approximately 12%) of persistent or recurrent gonorrhea or chlamydial infection. Failure to ensure treatment of sex partners is thought to be one major cause of recurrent infection, and the management of sexually transmitted infections should include ensuring the treatment of patients' sex partners. Although gonorrhea and chlamydia are both reportable infections in all U.S. states, most U.S. health departments do not make any routine effort to contact people diagnosed with gonorrhea or chlamydial infection, and clinicians should regard partner treatment as part of their responsibility when treating patients. The best course of action here is to ask the patient to bring her partner to your office for treatment when she comes for her ceftriaxone injection. If she does not bring the partner when she returns, you should offer her patient-delivered partner therapy (PDPT) with cefixime 400 mg and azithromycin 1 g at that time. PDPT is now legal in most parts of the United States and is recommended as a routine option in the Centers for Disease Control and Prevention (CDC) treatment guidelines for sexually transmitted diseases. PDPT should be dispensed with written information about sexually transmitted infections and the drugs being provided. Helpful links for additional resources related to PDPT are available:

CDC website on expedited partner therapy, including information about the legal status of PDPT in different states: <http://www.cdc.gov/STD/ept/legal/default.htm>

Washington State Department of Health EPT website: <http://www.doh.wa.gov/YouandYourFamily/IllnessandDisease/SexuallyTransmittedDisease/ExpeditedPartnerTherapy.aspx>. Includes information sheets for patients.

3. A 30-year-old man who you have seen several times during the last few years comes to your office complaining of a urethral discharge and dysuria for 3 days. The patient only has sex with other men and reports two sex partners in the last 2 months; he uses condoms inconsistently. He has a purulent discharge on physical examination. You treat him with ceftriaxone and azithromycin, both of which he receives while in your office. He has positive nucleic acid amplification test (NAAT) results demonstrating both urethral and pharyngeal gonorrhea. His test results for *Chlamydia trachomatis*, syphilis, and HIV infection are all negative. He returns to see you 10 days later because he still has discomfort when he urinates. He reports that the discharge from his penis has improved but not resolved. On examination, his discharge is scant and cloudy, not overtly purulent. He denies having sex, including oral sex, since his treatment. A sample of the initial 30 mL of voided urine is leukocyte esterase positive. How do you manage this patient?

- A. Treat him again with ceftriaxone 250 mg IM and azithromycin 1 g.
- B. Perform a urethral culture and NAAT for gonorrhea.
- C. Treat him with moxifloxacin 400 mg PO for 7 to 14 days.
- D. Treat him with metronidazole 2 g PO once.
- E. B and C

Answer: E Patients presenting with persistent symptoms of urethritis should have a Gram stain or, if that is not available, leukocyte esterase testing of their urine to identify objective evidence of inflammation. This patient has a positive leukocyte esterase test result and a visible discharge, establishing a diagnosis of persistent or recurrent urethritis. The differential diagnosis here includes

reinfection, treatment failure related to gonorrhea, and persistent urethritis due to a cause other than gonorrhea. Although reinfection is always a possibility in patients whose symptoms do not completely resolve, this patient denies having sex since his treatment. Treatment failure is also possible.

Treatment failure related to gonococcal resistance is now an important concern, and treatment failures have been observed, particularly among persons treated with an oral cephalosporin (i.e., cefixime) without concurrent azithromycin therapy. However, treatment failure with ceftriaxone, although conceivable, remains unlikely, given the current epidemiology of gonococcal resistance in the United States, and testing for persistent gonorrhea with both culture and a NAAT is a reasonable course of management for this patient. A positive culture for *Neisseria gonorrhoeae* would establish the diagnosis of gonorrhea, whereas a negative NAAT result would rule that diagnosis out. A positive NAAT result could reflect either persistent infection or simply the continued presence of RNA or DNA, which can persist in the absence of active infection for 7 to 21 days. Thus, a positive NAAT result with a negative culture would not establish a definitive diagnosis. Persons with possible gonorrhea treatment failures should have antimicrobial susceptibility testing performed on a cultured specimen and receive a second course of ceftriaxone 250 mg IM and azithromycin 1 g while awaiting antimicrobial susceptibility test results. The most likely diagnosis in this patient is persistent urethritis due to a pathogen that was not treated with the initial antimicrobial regimen. The most common identifiable cause of persistent urethritis in MSM is *Mycoplasma genitalium*. No Food and Drug Administration–approved commercial test is widely available for *M. genitalium*. Neither azithromycin nor doxycycline is consistently effective against this pathogen, and β -lactam antibiotics do not have activity against the organism. The best therapy for persistent urethritis in MSM is moxifloxacin 400 mg PO qd for 7 to 14 days. The CDC recommends 7 days, but treatment failures have been reported with that regimen, and longer courses may be superior. Clinicians should consider adding metronidazole 2 g PO in a single dose to the therapy for persistent urethritis in heterosexuals to treat *Trichomonas vaginalis*; *Trichomonas* is very uncommon in MSM, like the patient described here.

4. A 21-year-old woman comes to your office complaining of mild low abdominal pain and vaginal discharge for 2 weeks. She denies fever, chills, nausea, vomiting, or diarrhea and has no significant past medical history. She has had an intrauterine device (IUD) in place for 2 years. She has been monogamous with a new male partner for 2 months; they used condoms for vaginal sex for 1 to 2 weeks but not since then. Her most recent sexual contact before starting her current relationship was 7 to 8 months ago. On physical examination, the patient is afebrile and well appearing. She has mild bilateral lower abdominal tenderness without rebound tenderness; her bowel sounds are normal. Her pelvic examination is notable for a yellow discharge coming out of the cervical os, cervical motion tenderness, and mild bilateral adnexal tenderness without palpable masses. How do you manage this patient?

- A. Test her for gonorrhea and chlamydial infection and treat her with ceftriaxone 250 mg IM once, doxycycline 100 mg PO bid for 14 days, and metronidazole 500 mg PO bid for 14 days.
- B. Arrange to see the patient again or speak to her by telephone in 48 to 72 hours to ensure that her symptoms are improving.
- C. Admit her to the hospital for parenteral therapy with IV cefoxitin and oral or IV doxycycline.
- D. Arrange to have her IUD removed.
- E. A and B

Answer: E This patient has signs and symptoms consistent with mucopurulent cervicitis and mild pelvic inflammatory disease (PID). *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are the main sexually transmitted pathogens, but neither can be identified in half or more of women with PID. PID is often considered to be a polymicrobial infection, but the role of anaerobic bacteria and the importance of treating patients with mild or moderate PID (e.g., without overt pyosalpinx or pelvic abscess) for anaerobes is controversial. Therefore, the addition of metronidazole to the patient's treatment regimen is optional. This patient does not require hospital admission but should have follow-up in the 48 to 72 hours after treatment to ensure that she is improving. An IUD called the Dalkon Shield was associated with PID many years ago, and IUD insertion is a risk factor for PID in women with

gonorrhea or chlamydia at the time of device insertion. However, the diagnosis of PID does not mandate IUD removal in women with an IUD in place. At the same time, few data are available on the risk of recurrent PID in women using IUDs, and the presence of an IUD in this patient is an additional reason for close medical follow-up.

Ch / 300 **HAEMOPHILUS AND MORAXELLA INFECTIONS**

1. Which of the following statements about *Haemophilus influenzae* is true?

- A. It is a gram-positive bacterium that commonly causes skin infections in infants, children, and older adults.
- B. It is a gram-negative bacterium that commonly causes respiratory tract infections in infants, children, and older adults.
- C. It is a gram-negative bacterium that can be isolated on and grows easily on MacConkey's agar plates without blood or other supplements.
- D. It is a virus that causes epidemic influenza infections.

Answer: B *H. influenzae* is a gram-negative bacterium that causes respiratory and invasive infections in infants, children, and older adults. It is fastidious and grows best on chocolate agar in a carbon dioxide-enriched environment. It was originally recovered from patients with influenza and was considered the cause of that disease, hence its name. (See section on the pathogen.)

2. Which of the following statements about human host defenses against *Haemophilus influenzae* is true?

- A. Cell-mediated immunity is the most important host defense against infection.
- B. Antibody directed against the cell wall and complement are the most important host defenses against infection.
- C. Antibody against the cell capsule and complement are the most important host defenses against infection.
- D. Complement plays no role in host defense against infection.

Answer: C Antibody directed against the cell capsule and complement provide bactericidal immunity to *H. influenzae*. Subjects lacking either are at risk of invasive infection. Complement is an essential component of host defenses against some *H. influenzae* diseases, and complement deficiency states predispose to infection with the organism. (See section on pathobiology.)

3. Which of the following statements about treatment of *Haemophilus influenzae* infections is true?

- A. Ampicillin is the initial treatment of choice for infection pending results of susceptibility tests in the laboratory.
- B. Chloramphenicol is the initial treatment of choice for infection pending results of susceptibility tests in the laboratory.
- C. Rifampin is the treatment of choice pending results of susceptibility tests in the laboratory.
- D. A third-generation cephalosporin (e.g., ceftriaxone) is the treatment of choice pending results of susceptibility tests in the laboratory.

Answer: D Many strains of *H. influenzae* produce β -lactamases that inactivate ampicillin, and the prevalence of ampicillin resistance has increased dramatically. An inactivating enzyme, chloramphenicol acetyltransferase, causes resistance to that antibiotic. Rifampin is the treatment of choice for prophylaxis of nonimmunized contacts but not for established infection. (See sections on treatment and prevention.)

4. Which of the following statements about prevention of *Haemophilus influenzae* infections is true?
- A. The unconjugated Hib polysaccharide vaccine has been effective in preventing otitis, meningitis, and bacteremic *H. influenzae* type b infections in infants, toddlers, children, and adults.
 - B. The conjugated Hib polysaccharide vaccine has been effective in preventing otitis, meningitis, and bacteremic *H. influenzae* type b infections in infants, toddlers, children, and adults.
 - C. The conjugated Hib polysaccharide vaccine has been effective in preventing otitis, meningitis, and bacteremic all serotypes of *H. influenzae* infections in infants, toddlers, children, and adults.
 - D. Vaccines are generally ineffective in preventing *H. influenzae* type b infection, and rifampin is the only effective prophylactic treatment.

Answer: B The conjugated vaccine protects infants, children, and, by reducing the carrier state, older adults against invasive *H. influenzae* infections. (See section on prevention.)

5. Which of the following statements about *Moraxella catarrhalis* infections is true?
- A. *M. catarrhalis* is a commensal of the respiratory tract and rarely causes infection.
 - B. *M. catarrhalis* is commonly associated with bacteremia and meningitis.
 - C. *M. catarrhalis* is commonly associated with exacerbations of chronic bronchitis.
 - D. *M. catarrhalis* is commonly found in the respiratory tract of pet animals including dogs and cats and is transmitted from them to humans, in whom it can cause disease.

Answer: C New strains of *M. catarrhalis* are commonly associated with exacerbations of chronic bronchitis, and treatment of these speeds recovery. (See section on *Moraxella* infections).

Ch / 301 CHANCROID

1. Which of the following drugs would not be used to empirically treat a patient with suspected chancroid?
- A. Ampicillin
 - B. Erythromycin
 - C. Ciprofloxacin
 - D. Ceftriaxone
 - E. Azithromycin

Answer: A Most strains of *Haemophilus ducreyi* harbor plasmids that encode β -lactamase. Although there are few data on the current state of antibiotic resistance in *H. ducreyi*, there have been few reports of resistance to quinolones, macrolides, or third-generation cephalosporins.

The following scenario applies to questions 2, 3, and 4.

A 28-year-old man who recently traveled to Africa presents with two painful, large genital ulcers and inguinal lymphadenopathy. He states that he had sex with a bar worker during the trip and subsequently had sex with his usual partner when he returned home before he noted symptoms. The lesions evolved during a period of 3 weeks. A dark-field examination for *Treponema pallidum* and a polymerase chain reaction (PCR) analysis for herpes simplex virus of the ulcer exudate are negative.

2. Serologic tests that should be ordered in this situation include those for
- A. HIV-1
 - B. Syphilis
 - C. *H. ducreyi*
 - D. Both A and B
 - E. A, B, and C

Answer: D All patients with genital ulcer disease should be tested for HIV-1 and syphilis. There are no serologic tests for *H. ducreyi*.

3. Presumptive therapy should be given with

- A. Doxycycline for suspected lymphogranuloma venereum
- B. Acyclovir for suspected herpes simplex
- C. Benzathine penicillin for suspected syphilis
- D. A 3-week course of azithromycin for suspected granuloma inguinale
- E. A single dose of azithromycin for suspected chancroid

Answer: E Provided his syphilis serologic test result is also negative, the patient has met clinical criteria for a presumptive diagnosis of chancroid; a single 1-g dose of oral azithromycin has cure rates of more than 90%.

4. His regular partner should be

- A. Notified and be told to seek care if she develops symptoms
- B. Notified and be examined but not treated if there are no lesions
- C. Notified, be examined, and be treated regardless of the presence or absence of lesions or laboratory findings
- D. Notified only if the patient consents
- E. Notified, be examined, and be treated only if she has laboratory confirmation of infection

Answer: C The estimated transmission rate of *H. ducreyi* from infected men to women is 70%. As is true for all bacterial agents of sexually transmitted infections, all contacts should be notified, be examined, have a laboratory evaluation, and be treated regardless of clinical or laboratory findings.

5. The most sensitive and specific method for diagnosis of *H. ducreyi* infection is

- A. Gram stain of the ulcer exudate
- B. PCR-based test of a swab of the exudate
- C. The typical clinical findings of large, nonindurated ulcers with inguinal lymphadenitis
- D. Culture of the exudate
- E. Direct fluorescence microscopy with specific antibodies

Answer: B PCR has a high sensitivity and specificity for *H. ducreyi*; culture is 100% specific but at most 75% sensitive. The other modalities hover in the 50% sensitivity and specificity range.

1. Cholera is an acute diarrheal disease caused by

- A. *Vibrio cholerae* O1 and *Vibrio cholerae* O139
- B. *Vibrio cholerae* O1 only
- C. *Vibrio cholerae* O139 only
- D. Non-O1 *Vibrio cholerae*
- E. *Vibrio vulnificus*

Answer: A Cholera is the disease caused by both O1 *V. cholerae* and, since 1992, O139 *V. cholerae*. These two pathogens have the potential to cause local epidemics with pandemic potential.

2. The typical solute concentration of cholera stools, compared with plasma, is

- A. Hypertonic
- B. Hypotonic
- C. Isotonic
- D. Hyperosmolar
- E. Hypo-osmolar

Answer: C Typical diarrhea of cholera is isotonic compared with plasma, having almost the same concentration of sodium.

3. The benefit of using effective antimicrobials in patients with severe cholera is

- A. To reduce the excretion of vibrio
- B. To reduce the duration of diarrhea and volume of stool by half
- C. To reduce the duration of hospitalization by half
- D. To reduce the need for intravenous treatment
- E. To reduce the need for oral rehydration solutions

Answer: B Effective antimicrobials reduce the duration of diarrhea and the volume of stools by almost half compared with controls.

4. Intravenous fluids are indicated in patients with cholera under the following conditions:

- A. In every patient with cholera irrespective of the degree of dehydration
- B. In patients with some degree of dehydration
- C. In patients with severe dehydration, in those who cannot tolerate the oral route, and in those with high stool output
- D. In patients who do not respond to antimicrobials
- E. In those thought to be infected by resistant pathogens

Answer: C Intravenous fluids should be restricted to those with severe dehydration, to those with lesser degrees of dehydration who cannot tolerate the oral route, and to those with high stool output.

5. A patient with chronic liver disease presents to the emergency department with the acute onset of fever after ingestion of oysters. The physical examination reveals a patient in shock with multiple erythematous lesions on the extremities. The most likely pathogen involved is

- A. *Vibrio cholerae* O1
- B. *Vibrio cholerae* O139
- C. *Vibrio vulnificus*
- D. *Salmonella enterica*
- E. *Shigella dysenteriae* type 1

Answer: C *Vibrio vulnificus* is the most likely pathogen. It causes severe sepsis with soft tissue involvement in patients with chronic liver disease.

1. Which one of the following statements best characterizes the epidemiology of *Campylobacter jejuni*?
- A. *C. jejuni* gastroenteritis is common in developed countries such as the United States but uncommonly causes illness in developing nations.
 - B. In developing nations, the incidence of *C. jejuni* infection peaks during winter and spring.
 - C. In developed nations, the incidence of *C. jejuni* is higher in men than in women.
 - D. Most *C. jejuni* infections occur as a result of person-to-person transmission.
 - E. Most *C. jejuni* infections occur as part of outbreaks rather than as sporadic infections.

Answer: C *C. jejuni* infections are common in both developed and developing nations. In developed nations, infections peak in late summer and fall; in developing nations, no seasonality is observed. The incidence of infection in developed nations is higher in young men than in young women. Person-to-person transmission of infection is possible but not common. Most infections are sporadic. (See section on epidemiology.)

2. Which one of the following statements about the pathogenesis of *C. jejuni* is true?
- A. Microscopic examination of the bowel will show an inflammatory infiltrate consisting of neutrophils, mononuclear cells, and eosinophils in the lamina propria.
 - B. The incubation period is short, sometimes less than 4 hours from exposure to symptom onset.
 - C. Extracellular toxins are important in the pathogenesis of colitis associated with *C. jejuni* infections.
 - D. Development of long-term immunity after a single infection makes recurrent infections unlikely.
 - E. *C. jejuni* exerts its pathogenic effects on superficial intestinal mucosa only; invasion to deeper tissues does not occur.

Answer: A The incubation period is usually 2 to 4 days. Extracellular toxins are elaborated but are not important in pathogenesis. Immunity to infection is short-lived; one infection does not protect against future infections. (In developing nations where recurrent infections are common, asymptomatic infections may occur in adults.) *C. jejuni* infection is capable of invasion; that is why bacteremia occasionally occurs. (See section on pathobiology.)

3. The most common clinical manifestation of *C. jejuni* infection in developed nations is

- A. Asymptomatic infection
- B. Chronic, watery diarrhea
- C. Acute, self-limited diarrhea
- D. Guillain-Barré syndrome
- E. Sepsis

Answer: C Asymptomatic infections are unusual in developed nations, although they are more common in developing nations. Diarrheal illness is usually self-limited; chronic illness is not a typical feature of infection with this pathogen. Guillain-Barré syndrome is a rare complication of infection. Sepsis, although possible, also is rare. (See section on clinical manifestations.)

4. Which of the following preventive measures would be most likely to reduce the incidence of *C. jejuni* infections in developed nations?

- A. More consistent use of currently available vaccines
- B. Proper treatment of water from rivers or streams before being consumed by hikers and campers
- C. Exclusion of persons with diarrhea from work as food handlers
- D. Requirement that all eggs served in hospitals or other health care facilities be pasteurized
- E. Avoidance of eating undercooked chicken in both homes and restaurants

Answer: E There is not currently a commercially available vaccine. Consumption of untreated water from rivers and streams is a risk factor but is not as important a contributor to infection as is eating undercooked chicken. Although all persons with an acute diarrheal illness should be excluded from

work as food handlers, transmission from infected food handlers is not a big contributor to the incidence of *C. jejuni* infections. For example, transmission within households of infected persons is uncommon. Eggs served in hospitals should be pasteurized because of the risk of *Salmonella* infections; however, this is not likely to have a big impact on rates of *C. jejuni* infections. Consumption of undercooked chicken is the single most common risk factor for development of *C. jejuni* infections. (See section on prevention.)

5. Which one of the following antibiotics is the best choice for treatment of gastroenteritis caused by *C. jejuni* infection?

- A. Amoxicillin
- B. Azithromycin
- C. Cephalexin
- D. Gentamicin
- E. Chloramphenicol

Answer: B Penicillins and cephalosporins are not effective in the treatment of *C. jejuni*. Gentamicin is effective but not an appropriate choice for an uncomplicated gastrointestinal infection. Chloramphenicol also is effective, but the side effects associated with this drug make it a less accepted choice than azithromycin. (See section on treatment.)

Ch / 304 **ESCHERICHIA COLI ENTERIC INFECTIONS**

1. A previously healthy 22-year-old student returned home to Connecticut 2 days ago from a 2-week trip to southern India. She drank only bottled water but did eat food from street vendors. On her last day, she developed nausea followed by loose stools, which have persisted. On examination, she is afebrile with normal orthostatic vital signs and appears tired but otherwise well. Her abdomen is soft and nontender with increased bowel sounds. She has had four watery stools so far today. Which of the following is appropriate for her?

- A. Oral rehydration solution and azithromycin 500 mg PO daily for 3 days for presumed ETEC or EAEC traveler's diarrhea
- B. Stool ova and parasite examination and empirical metronidazole 500 mg three times a day for 7 days
- C. Stool culture; alert clinical laboratory to look for ETEC and EAEC
- D. Intravenous saline
- E. Blood cultures and stool cultures for typhoid fever

Answer: A Traveler's diarrhea is the most common treatable illness encountered by North American visitors to developing areas. The majority of cases are caused by diarrheogenic *E. coli*, particularly ETEC and EAEC. Empirical treatment with azithromycin is appropriate, and oral rehydration should be administered. This acute presentation is unlikely to be due to a protozoan, and examination by ova and parasite and empirical antiprotozoal therapy are inappropriate. A stool culture would be appropriate if she had a fever or bloody diarrhea to look for *Campylobacter*, *Shigella*, or *Salmonella*, but clinical laboratories cannot identify ETEC or EAEC. Intravenous rehydration would be appropriate only in the setting of significant volume depletion and inability to consume oral rehydration fluid. Whereas India is endemic for typhoid fever, this illness rarely is manifested with acute diarrhea in the absence of fever.

2. How is infection with diarrheogenic *E. coli* most commonly acquired?

- A. Ingestion of food or water that was contaminated with virulent *E. coli* and maintained at a temperature favorable for replication of organisms to an infectious dose
- B. Exposure to fecal material from an infected person (e.g., changing diapers)
- C. Transfer of genetic material encoding toxins or adherence factors from pathogenic species to commensal *E. coli* within the gut
- D. Ingestion of food containing preformed heat-stable or heat-labile toxins from *E. coli*
- E. Spread of virulent *E. coli* from other body sites (urinary tract or skin) through hematogenous or direct extension of infectious foci

Answer: A With the exception of EHEC, diarrheogenic *E. coli* have a high infectious dose, meaning that they must be present in large concentrations to establish disease. This is usually achievable only through environmental replication within contaminated food or water, in contrast to EHEC, which can be spread person to person. Whereas virulence genes are readily transferred between bacteria, diarrheogenic strains are distinct from commensal *E. coli* and generally exist in a relatively limited number of related phylogenetic groups. Unlike *Staphylococcus aureus* and *Clostridium perfringens* enterotoxins, the ETEC enterotoxins are produced by live organisms after they reach and adhere to the small bowel epithelium. Most diarrheogenic *E. coli* are distinct from the strains adapted to cause invasive infections, such as bacteremia, meningitis, or pyelonephritis (although many DAEC and some EAEC are phylogenetically related to uropathogenic *E. coli*).

3. An *E. coli* clone is isolated in high concentrations in stool from several patients with nonbloody diarrhea. The organism is able to adhere to HeLa cells in tissue culture but does not produce actin pedestals. Genetic analysis of the organism reveals it to be negative for AA, Afa/Dr, ST, LT, and LEE genes but positive for the SLT-1 (Stx1) and SLT-2 (Stx2) genes. To which pathotype does this organism likely belong?

- A. Enterotoxigenic *E. coli* (ETEC)
- B. Enteroaggregative *E. coli* (EAEC)
- C. Enterohemorrhagic *E. coli* (EHEC)
- D. Shigatoxigenic *E. coli* (STEC)
- E. Enteropathogenic *E. coli* (EPEC)

Answer: D The ability to adhere to HeLa cells suggests the possibility of pathogenicity, but the lack of actin pedestals and LEE genes rules out EPEC and EHEC. The organism does not express the AA plasmid of EAEC, the Afa/Dr adhesin of DAEC, or the ETEC toxins. However, it does express the Shiga-like toxins, making it a non-EHEC STEC strain. These strains can cause bloody or nonbloody diarrhea or can be nonpathogenic.

4. A 6-year-old previously healthy boy is admitted with 1 day of watery and then bloody diarrhea and abdominal cramps. His temperature is 37.3° C, and he has mild tachycardia. Results of laboratory tests on admission show an elevated white blood cell count of 14.4 with 85% neutrophils. Stool culture results are pending. What is the appropriate empirical antimicrobial while awaiting stool culture results?

- A. Ciprofloxacin PO
- B. Trimethoprim-sulfamethoxazole PO
- C. Ceftriaxone IV
- D. Azithromycin PO
- E. No antibiotics should be given

Answer: E This is a typical presentation of hemorrhagic colitis due to EHEC or STEC. Antibiotics are not recommended in this disease because there is inadequate proof that they are beneficial, and in fact a number of studies have shown an association with increased risk of hemolytic-uremic syndrome. Fluoroquinolones and trimethoprim-sulfamethoxazole, in particular, have been shown to increase SLT production. Whereas azithromycin was shown to reduce shedding of O104:H4 ST/EAEC, its use was

not shown to reduce hemolytic-uremic syndrome risk. Although this child could have *Shigella* or *Campylobacter* infection, the lack of fever makes these less likely, and a 1-day delay in antibiotic administration until culture results return would not be harmful, given that antibiotics have a relatively small effect on those self-limited infections.

5. Which of the following would have the greatest global impact on reducing *E. coli* diarrhea infections?
- A. Universal vaccination with the killed cholera/*E. coli* LT-B vaccine
 - B. Universal vaccination of commercial livestock with the EHEC veterinary vaccine
 - C. Universal antibiotic prophylaxis of travelers to developing areas
 - D. Universal ban on antibiotic use in animal feed
 - E. Universal provision of treated potable water to developing areas

Answer: E The greatest burden of all diarrheal illness, and of *E. coli* in particular, is in children in developing areas who lack regular access to treated water. The ETEC vaccine and antibiotic prophylaxis, although somewhat effective in reducing the risk of traveler's diarrhea, offer only short-term protection. The EHEC veterinary vaccine might reduce human cases of EHEC associated with contamination of food and water, but EHEC, fortunately, remains largely a rare concern and occurs mostly in developed countries. Because most *E. coli* enteric infections do not require antibiotic treatment, the emergence of antibiotic resistance due to overuse of antibiotics in people and commercial livestock is less of a concern for diarrheogenic *E. coli* than for invasive *E. coli* and other important infections.

1. A 78-year-old man was admitted to a surgical intensive care unit in New York City for management of severe, necrotizing pancreatitis. He was empirically treated with meropenem. On the 18th day of surgical intensive care unit admission, while still receiving meropenem, he developed a fever (temperature of 39.5° C) and hypotension requiring inotropic support. Blood culture samples were collected, and nonmotile gram-negative bacilli were seen after incubation for 12 hours. Which of the following statements about management of the bacteremia is true?
- A. He should receive ampicillin for a likely *Enterobacter cloacae* blood stream infection.
 - B. He should receive ampicillin-sulbactam for a likely *Escherichia coli* blood stream infection.
 - C. He should be maintained on meropenem for a likely ESBL-producing *Klebsiella pneumoniae* blood stream infection.
 - D. He should receive a polymyxin in combination with other antibiotics for blood stream infection because of a probable carbapenem-resistant organism.
 - E. His antibiotics should be discontinued and the blood stream infection should be managed by changing all intravascular lines.

Answer: D Carbapenem-resistant gram-negative organisms are now endemic in many parts of the world. Carbapenem resistance, mediated by the KPC carbapenemase, is widespread in many parts of the United States, Greece, Italy, and Israel. This creates significant management issues for severe sepsis due to gram-negative bacilli. At present, a polymyxin in combination with meropenem or tigecycline is the treatment of choice for KPC producers. Source control should also be used, when appropriate.

2. A 27-year-old woman has a history of recurrent urinary tract infections. She presents with symptoms of dysuria and urinary frequency. *Escherichia coli* is isolated from her urine and is found to be resistant to ampicillin, trimethoprim-sulfamethoxazole, and ciprofloxacin. The organism is susceptible to piperacillin-tazobactam and ertapenem. Which of the following scenarios is most likely?

- A. TEM-1 accounts for the resistance to ciprofloxacin.
- B. NDM-1 accounts for the resistance to trimethoprim-sulfamethoxazole.
- C. She is most likely infected with the ST171 strain of *E. coli*.
- D. She is most likely infected with the ST131 strain of *E. coli*.
- E. She most likely works in a New York City nursing home and has infection with KPC-producing *E. coli*.

Answer: D ST131 *E. coli* is an international pandemic clone that is typically resistant to ciprofloxacin. It may also be ESBL producing due to production of the CTX-M-15 β -lactamase. Although there are reports of ST131 producing carbapenemases, this is not commonplace.

3. A 24-year-old medical student undertakes an elective in Nepal. While there, he goes mountain climbing but falls and breaks his leg. After undergoing surgery in Kathmandu, he is transferred back to the United States after 2 weeks of hospitalization in Nepal. A rectal swab is taken on admission to the hospital in the United States. Which of the following are most likely to be found?
- A. NDM-producing *Klebsiella pneumoniae*
 - B. KPC-producing *Klebsiella pneumoniae*
 - C. AIM-1-producing *Klebsiella pneumoniae*
 - D. VIM-1-producing *Klebsiella pneumoniae*
 - E. IMP-4-producing *Klebsiella pneumoniae*

Answer: A NDM-producing organisms are endemic in many hospitals in the Indian subcontinent. Patients hospitalized in this area may become colonized with NDM producers. They may then serve as reservoirs for these organisms when transferred to hospitals in countries without endemic NDM producers. Outbreaks may result unless adequate infection control interventions are used.

4. A 66-year-old man has been ventilated for 3 weeks after a severe head injury. He develops radiologic changes in his chest consistent with right middle and lower lobe consolidation. His endotracheal aspirates have become purulent, and he has developed a new fever. The laboratory identifies a motile gram-negative bacillus. It is able to ferment sugars. It is oxidase negative. On susceptibility testing, it is resistant to ampicillin and ceftazidime but susceptible to ciprofloxacin, gentamicin, and meropenem. The most likely organism is
- A. *Pseudomonas aeruginosa*
 - B. *Staphylococcus aureus*
 - C. *Streptococcus pneumoniae*
 - D. *Acinetobacter baumannii*
 - E. *Enterobacter cloacae*

Answer: E The Enterobacteriaceae are able to ferment sugars, whereas “nonfermenters” like *P. aeruginosa* (an oxidase-positive organism) and *A. baumannii* (an immotile organism) are not. Staphylococci and streptococci are gram-positive organisms. Only *E. cloacae* fits the description.

1. Which of the following bacteria is most commonly associated with hospital-acquired infections in the United States?

- A. *Stenotrophomonas maltophilia*
- B. *Burkholderia cepacia*
- C. *Pseudomonas aeruginosa*
- D. *Burkholderia mallei*
- E. *Burkholderia pseudomallei*

Answer: C Data from the National Healthcare Safety Network at the Centers for Disease Control and Prevention indicate that during 2009 to 2010, *P. aeruginosa* was responsible for 8% of a total of 69,475 hospital-acquired infections and was the sixth most frequent culprit among 81,139 pathogens. *S. maltophilia* is a pathogen responsible for hospital-acquired infections but ranks lower in frequency than *P. aeruginosa*. *B. pseudomallei* and *B. mallei* are not causes of hospital-acquired infections in the United States. However, these pathogens are bioterrorism factors. *B. B. cepacia* is an important emerging pathogen that is associated with hospital-acquired infections in immunocompromised patients beyond its established role as a pathogen in cystic fibrosis patients. *B. cepacia* hospital-acquired infections rank much lower in frequency than hospital-acquired infections due to *P. aeruginosa*.

2. Which of the following statements regarding *Pseudomonas aeruginosa* is true?

- A. It is a nonmotile gram-negative bacterium.
- B. It is not the only cause of ecthyma gangrenosum.
- C. Endocarditis due to the *P. aeruginosa* is always associated with high fever.
- D. Ertapenem is effective as treatment against *P. aeruginosa*.
- E. Tigecycline is effective as treatment against *P. aeruginosa*.

Answer: B Other causes of ecthyma gangrenosum include *Staphylococcus aureus*, *Aeromonas hydrophila*, *Klebsiella pneumoniae*, *Morganella morganii*, *Stenotrophomonas maltophilia*, *Citrobacter freundii*, and fungi (*Candida albicans*, *Aspergillus fumigatus*). *P. aeruginosa* is a motile bacterium. Ertapenem and tigecycline are not effective treatment against *P. aeruginosa*. Endocarditis due to *P. aeruginosa* is usually more indolent than endocarditis due to *S. aureus*. It is not always associated with high fever.

3. Which of the following patient groups is at increased risk for the development of *P. aeruginosa* infections?

- A. Neutropenic patients
- B. Patients with cystic fibrosis
- C. Patients with Charcot's arthropathy
- D. Patients requiring mechanical ventilation
- E. All the above

Answer: E Neutropenia, Charcot's arthropathy, mechanical ventilation, and also burns, cystic fibrosis, cancer, transplantation, diabetes, steroid treatment, foreign bodies, hypogammaglobulinemia, and AIDS are associated with an increased risk for *P. aeruginosa* infection.

4. Which of the following is considered the drug of first choice for *Stenotrophomonas maltophilia*?

- A. Doxycycline
- B. Meropenem
- C. Trimethoprim-sulfamethoxazole
- D. Ciprofloxacin
- E. Ceftazidime

Answer: C *S. maltophilia* has inherent resistance to carbapenems. Trimethoprim-sulfamethoxazole is the choice for first-line treatment. Ciprofloxacin and ceftazidime have been used in the treatment of *S. maltophilia* infections either alone or in combination but are not first-choice treatment. Tetracyclines have some activity against *S. maltophilia* but are not first-choice options for treatment.

5. The following are true regarding infection due to *Burkholderia pseudomallei* except which one?
- A. Southeast Asia, Australia, the Indian subcontinent, and Sri Lanka are locations with an increased risk for this infection.
 - B. Risk factors for infection include renal failure, diabetes mellitus, and heavy alcohol consumption.
 - C. The infection is called melioidosis.
 - D. An extended eradication regimen with oral trimethoprim-sulfamethoxazole for 1 month is necessary to follow initial intravenous treatment.
 - E. Recurrence of melioidosis is due to reactivation.

Answer: D An extended oral eradication regimen with oral trimethoprim-sulfamethoxazole for 3 to 6 months (not only 1 month) is recommended to follow initial intravenous treatment for the treatment of melioidosis.

Ch / 307 DISEASES CAUSED BY ACINETOBACTER AND STENOTROPHOMONAS SPECIES

1. Your patient has a blood culture turn positive. The preliminary result from the laboratory indicates possible *Acinetobacter baumannii*. Which of the following agents is most likely to have in vitro activity against *A. baumannii*?
- A. Ertapenem
 - B. Ampicillin-sulbactam
 - C. Piperacillin-tazobactam
 - D. Trimethoprim-sulfamethoxazole
 - E. Doxycycline

Answer: B Increasing resistance to a variety of antimicrobial agents complicates the treatment of *Acinetobacter* species infections today. When it is susceptible, *Acinetobacter* is typically treated with sulbactam (in the formulation of ampicillin-sulbactam in the United States at a dose of 3 g intravenously every 6 hours). Other options are the carbapenems imipenem and meropenem and the broad-spectrum cephalosporins. See treatment section under *Acinetobacter* species.

2. Your patient has a blood culture turn positive. The preliminary result from the laboratory indicates possible *Stenotrophomonas maltophilia*. Which of the following agents is most likely to have in vitro activity against *S. maltophilia*?
- A. Ertapenem
 - B. Ampicillin-sulbactam
 - C. Piperacillin-tazobactam
 - D. Trimethoprim-sulfamethoxazole
 - E. Meropenem

Answer: D *S. maltophilia* is an increasingly important cause of the nosocomial infections, and it exhibits intrinsic resistance to many antibiotics. Nevertheless, trimethoprim-sulfamethoxazole remains the drug of choice, at a dose of 10 to 15 mg/kg/day intravenously, based on the trimethoprim component, and it is given for 14 days or longer with positive blood cultures. See treatment section under *Stenotrophomonas maltophilia*.

3. Your patient has been admitted to the intensive care unit because of respiratory failure. He is intubated and mechanically ventilated. The intensive care unit is in the midst of an *Acinetobacter* outbreak. What would be the most effective intervention to decrease risk for development of an infection due to *Acinetobacter* in your patient?

- A. Extubate the patient and remove him from mechanical ventilation as soon as possible.
- B. Institute contact precautions (i.e., gowns and glove precautions).
- C. Prescribe prophylaxis for the patient with intravenous imipenem.
- D. Clean frequently touched objects in the patient's room with bleach.
- E. Prescribe prophylaxis for the patient with *Saccharomyces* through a nasogastric tube.

Answer: A During outbreaks in the hospital, cohorting of patients and use of dedicated staff to care for the cohorted patients might be necessary to control spread. Removal of indwelling devices from the patients, including vascular catheters and endotracheal tubes, can help prevent colonization and infection with *Acinetobacter*. See prevention section under *Acinetobacter* species.

4. You are managing a patient with a deep wound infection resulting from a combat injury that occurred in Iraq. After incision and drainage, preliminary results from operative cultures indicate growth of possible *A. baumannii*. The patient has an anaphylactic reaction to β -lactam antibiotics. Which agent would be most likely to be an effective therapeutic agent for the patient?

- A. Aztreonam
- B. Ciprofloxacin
- C. Tigecycline
- D. Chloramphenicol
- E. Rifampin

Answer: C Since initial reports of the outbreak of *A. baumannii* among military personnel in Iraq and Afghanistan, reports of severe wound infections and skin and soft tissue infections by this pathogen have increased in frequency. Multiple drug resistance and the presence of copathogens frequently complicate treatment. Most cases require surgical débridement and are associated with substantial mortality. Tigecycline might be the only available agent with in vitro activity against this pathogen in this setting. See the section on wound, burn, and skin and soft tissues infections under clinical manifestations of *Acinetobacter* species.

5. Your patient with cystic fibrosis has colonization of the respiratory tract with *Stenotrophomonas maltophilia*. The patient asks you what the significance of this colonization is and what can be done. Which of the following is the most accurate answer?

- A. Because *Stenotrophomonas* is only a colonizer, there is no association with poor outcomes.
- B. Treatment of colonization with an active antimicrobial improves the outcomes of cystic fibrosis patients.
- C. *Stenotrophomonas* increases mortality risk among cystic fibrosis patients primarily by causing necrotizing pneumonia.
- D. Pneumonia due to *S. maltophilia* in a patient with cystic fibrosis is an indication for lung transplantation.
- E. Colonization with *S. maltophilia* among patients with cystic fibrosis has been associated with reduction in lung function.

Answer: E Colonization or infection with *S. maltophilia* among patients with cystic fibrosis has been associated with reduction in lung function. See reference 15 and the epidemiology section under *Stenotrophomonas maltophilia*.

1. Regarding antimicrobial resistance among *Salmonella* Typhi isolated in the United States, which of the following is *true*?

- A. Ceftriaxone resistance occurs in the majority of strains.
- B. Decreased fluoroquinolone susceptibility is seen in more than a third of isolates.
- C. Multiple drug resistance is not observed.
- D. Gentamicin is an appropriate choice for treatment of enteric fever.
- E. The clinical microbiology laboratory will be unable to provide susceptibility results for azithromycin.

Answer: B Among U.S. *Salmonella* Typhi isolated during 1999 to 2006, less than 1% were resistant to ceftriaxone, 38% showed decreased fluoroquinolone susceptibility, and 13% were multidrug resistant (resistant to the traditional first-line antimicrobials ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole). For *Salmonella*, aminoglycosides may appear active *in vitro* but are not effective clinically. The Clinical Laboratory and Standards Institute (CLSI) published breakpoints and interpretive criteria for azithromycin and *Salmonella* for the first time in 2015.

2. Which of the following statements about nontyphoidal *Salmonella* is *false*?

- A. Typhimurium and Enteritidis are the most common nontyphoidal *Salmonella* serovars isolated in most high-income countries.
- B. Chickens are common reservoirs of *Salmonella* Enteritidis.
- C. *Salmonella* Dublin has a great propensity to cause blood stream infection.
- D. *Salmonella* Typhimurium is a human host-restricted serovar.
- E. Produce is an increasingly important source of nontyphoidal *Salmonella* infection.

Answer: D *Salmonella* Typhimurium and *Salmonella* Enteritidis are the most commonly isolated nontyphoidal *Salmonella* from the stool of humans with diarrhea. Chickens are major reservoirs of *Salmonella* Enteritidis. *Salmonella* Dublin is commonly isolated from blood. *Salmonella* Typhi and *Salmonella* Paratyphi, but not *Salmonella* Typhimurium, are human host-restricted serovars. Uncooked produce eaten fresh is an increasingly important source of nontyphoidal *Salmonella*. This may be related to fecal contamination of produce by animals.

3. A previously healthy 23-year-old male chef develops diarrhea. Stool culture grows *Salmonella* Typhimurium but the diarrhea persists. Which of the following is the most appropriate recommendation?

- A. Treat with ciprofloxacin.
- B. Prescribe loperamide.
- C. Encourage fluid and electrolyte replacement.
- D. Suggest that he continue work if he has no fever.
- E. Administer vaccine for typhoid fever.

Answer: C Nontyphoidal *Salmonella* diarrhea is usually self-limited in healthy, immunocompetent persons who are not at the extremes of age. Antimicrobials prolong *Salmonella* shedding. Drugs with antiperistaltic effects can prolong diarrhea and should be used sparingly. Individuals with diarrhea should be excluded from food handling. Typhoid vaccine does not protect against *Salmonella* Typhimurium infection.

4. A 36-year-old woman develops fever and abdominal pain after a trip to a typhoid-endemic country. Which of the following recommendations is most appropriate?

- A. Order a Widal test.
- B. Prescribe ampicillin for empirical treatment of typhoid fever.
- C. Collect blood culture specimens.
- D. Arrange for bone marrow culture.
- E. Administer dexamethasone.

Answer: C Blood culture represents the conventional standard diagnostic test for typhoid fever. Bone marrow culture is more sensitive than blood culture, but it is not often used as the first test. The Widal test and other serologic approaches to typhoid fever perform poorly. The high prevalence of ampicillin resistance in *Salmonella* Typhi and *Salmonella* Paratyphi make it a poor choice for empirical treatment. Any role for dexamethasone for treatment of typhoid fever is restricted to carefully selected patients with severe disease.

5. A 45-year-old woman with a history of blood culture–confirmed typhoid fever continues to have stool cultures that grow *Salmonella* Typhi 18 months after her initial illness despite remaining well. Which of the following recommendations is *not* appropriate?

- A. Do nothing because the patient feels well.
- B. Treat her with antimicrobials for *Salmonella* Typhi chronic carriage.
- C. Encourage handwashing.
- D. Exclude the patient from food handling.
- E. Determine whether she has gallbladder disease.

Answer: A This patient is a *Salmonella* Typhi chronic carrier because her stool culture is positive more than 12 months after the initial infection. Although she remains well, she continues to shed *Salmonella* Typhi in her stool, posing a risk for transmission to others. It is appropriate to treat her with antimicrobials suitable for the elimination of *Salmonella* Typhi carriage and to promote handwashing. She should be excluded from food preparation until she is demonstrated to no longer be a carrier. Gallbladder disease is a risk factor for the development of the chronic carrier state, although it is doubtful that the carrier state is a sufficient indication for cholecystectomy.

Ch / 309 SHIGELLOSIS

1. Spread of shigellosis can be difficult to control because the major route of transmission of infection is

- A. Food
- B. Water
- C. Person to person
- D. Aerosol
- E. Dirty toilet seats

Answer: C Because *Shigella* resist the antibacterial effects of gastric acid and invade intestinal epithelial cells, which protect them from immune mechanisms, the infectious inoculum can be very small, which eliminates the need to multiply before ingestion and facilitates direct (skin-to-skin) or indirect (by contaminated fomites) person-to-person spread. It is true that the organism can be transferred to food or water and subsequently cause outbreaks; however, transmission by these routes can be prevented by commonsense care around food preparation and chlorination of the water supply. *Shigella* are not respiratory pathogens and so aerosol transmission does not occur. Whereas transmission by dirty toilet seats is possible, acquisition of infection by this route has not been described.

2. The most common presentation of shigellosis in the United States is

- A. Watery diarrhea associated with fever
- B. Dysentery
- C. Hemolytic-uremic syndrome
- D. Leukemoid reaction
- E. Reactive arthritis

Answer: A The most common cause of shigellosis in the United States is *Shigella sonnei*, which only rarely proceeds beyond the watery diarrhea stage to bloody diarrhea or the dysentery syndrome. However, even *S. sonnei* induces an inflammatory enteritis with the production of pyrogenic cytokines such as interleukins 1, 6, and 8, and therefore elevated temperature is present in the majority of infected individuals. Some observations from experimentally infected adults suggest that the peak fever correlates with the severity of other clinical manifestations of shigellosis. The other options are all potential consequences of *Shigella* infection but largely found in cases due to either *Shigella flexneri* or *Shigella dysenteriae* type 1. *S. flexneri* in the United States is primarily found in cases involving men who have sex with men, who therefore often present with more severe presentations of shigellosis. *S. dysenteriae* type 1 is rarely found in the United States, and when such cases are identified, the infection has typically been acquired abroad.

3. The pathobiology of *Shigella* infection is a consequence of

- A. Activation of intestinal secretion pathways
- B. Lactose malabsorption
- C. Hyperperistalsis
- D. Mucosal edema
- E. Mucosal invasion and inflammation

Answer: E A hallmark of pathogenic shigellae is their ability to invade cells, including phagocytic leukocytes and nonphagocytic intestinal epithelial cells, by inducing a process analogous to phagocytosis. The release of pro-inflammatory cytokines during this process results in fever, recruitment of leukocytes to the intestinal mucosa, epithelial cell death and mucosal ulceration, and the characteristic finding of white and red blood cells in the stool. When the genes mediating these processes are deleted or experimental infections are treated with cytokine inhibitors, the severity of the typical clinical manifestations is attenuated.

Copious watery diarrhea, typically associated with the activation of specific ion secretion pathways in intestinal mucosa and characteristic of *Vibrio cholerae* infection, is not characteristic of shigellosis. The watery diarrhea induced by *S. sonnei*, for example, is not sufficient to cause serious dehydration, except in unusual cases. Lactose malabsorption is a consequence of damage to intestinal epithelial brush border membranes, where this disaccharidase is localized, and therefore may develop during and after clinical shigellosis, but it is not a cause of altered physiology underlying the infection. Inflammation of the colonic mucosa is common in shigellosis, manifested as cramps or, in severe cases, with bloody diarrhea or dysentery and tenesmus, but again, this is a consequence of the underlying inflammatory reaction. Rather than mucosal edema resulting from the myriad inflammatory pathways being activated, the histology of the affected intestine reveals leukocytic infiltration, blood, organisms in the submucosa and within epithelial cells, and mucosal ulcerations where dead epithelial cells have been sloughed off the mucosal surface.

4. The primary treatment of bloody diarrhea due to *Shigella* species is

- A. Oral rehydration fluids
- B. Intravenous rehydration fluids
- C. H₂ blockers
- D. Antibiotics such as ciprofloxacin (Cipro)
- E. Loperamide (Lomotil)

Answer: D Mild to moderate shigellosis presenting as watery diarrhea, and typically due to *S. sonnei*, is a self-limited illness, usually lasting only a couple of days and uncommonly the cause of significant dehydration requiring supervised rehydration by either the oral or the intravenous route. More severe clinical shigellosis, associated with bloody diarrhea, is uncomfortable because of the high frequency of bowel movements and associated cramps, and there is the potential for subsequent complications, depending on the etiologic agent involved. Antibiotic treatment with an agent to which the infecting organism is susceptible is well documented to resolve clinical symptoms and, if it is administered

early, to prevent late complications of shigellosis. The problem has been to administer a proven effective antibiotic to which the causative organism is susceptible because of the acquisition of multidrug resistance genes over time. At present, a quinolone such as ciprofloxacin (Cipro) or a macrolide such as azithromycin (Zithromax) is the most reliable choice as the prevalence of resistance is still low in most parts of the world, although it is not unknown and is slowly increasing.

Rehydration, by either oral rehydration solutions or intravenously administered fluids, is usually not necessary as the degree of dehydration in shigellosis is mild or is readily corrected if it is more significant. However, rehydration will not reverse the clinical manifestations due to inflammation and in this sense is a secondary consideration at best. H₂ blockers are known to increase the susceptibility to acid-sensitive enteric pathogens such as *V. cholerae* but not acid-resistant organisms like *Shigella* and have no effect on already established infections. Lomotil or other gut motility-inhibiting drugs such as Imodium that reduce peristalsis are, in fact, potentially dangerous in that they can prolong the contact between invasive *Shigella* and the mucosa and worsen the clinical severity of the infection. Where *S. flexneri* or *S. dysenteriae* type 1 is common, these drugs are in fact considered to be contraindicated, especially in children. In some studies, the combined use of ciprofloxacin and loperamide reduces the duration of symptoms or the number of stools passed compared with treatment with ciprofloxacin alone.

5. The best available way to prevent shigellosis is

- A. Immunization with *Shigella* vaccine
- B. High standards of personal and household hygiene
- C. Provision of prophylactic antibiotics to contacts of patients
- D. Quarantine
- E. Anti-inflammatory drugs

Answer: B Shigellosis is primarily contracted directly through fecal-oral transmission by the hands of an infected individual or indirectly by contaminated fomites to a susceptible individual. The way to break the cycle of transmission is to wash hands, especially when taking care of a patient with shigellosis (e.g., after handling soiled diapers or other clothes) or before preparing and serving food in the household. Additional measures, such as disinfecting the areas where soiled clothes are gathered with a simple disinfectant such as Lysol or diluted bleach, are also useful. Application of these measures within a household with an infected individual will reduce the transmission of infection to others in proximity to the index case. In other settings, such as developing countries with higher incidence and limited supplies of safe drinking water or facilities for the sanitary disposal of feces, use of hand sanitizers is useful and care in the consumption of nonbottled water or drinking of boiled water will be effective.

There is no available vaccine for shigellosis, although considerable effort has been expended to develop one that is both effective and safe. Prophylactic administration of antibiotics is a bad idea as hygiene is an effective way to prevent infection, and antibiotic exposure only increases the selective pressure for drug resistance to emerge. Quarantine is no longer a primary strategy for control of most infectious diseases because diagnosis and more specific measures can usually be implemented. Quarantine usually fails to prevent the spread of contagious diseases in the community as it is difficult to isolate all of the potential spreaders of infection. Whereas certain anti-inflammatory drugs (e.g., cytokine antagonists) have been shown to be effective in experimental models of shigellosis, none are currently available for clinical use.

1. A 44 year-old abattoir worker of Middle Eastern origin working in Ashtabula, Ohio develops fever and back pain over the past 2 weeks. He has three pet dogs at home. A standard tube agglutination (STA) shows a *Brucella* titer of 1 : 80. Which of the following is true regarding the diagnosis of *Brucella* in this patient?

- A. A single titer of 1 : 80 is sufficient to make the diagnosis of *Brucella* infection in this patient.
- B. This patient may have *Brucella canis* infection based on the positive STA titer result.
- C. The sensitivity of a blood culture at this time is about 30% and will likely increase with increasing length of illness.
- D. A bone marrow culture will be less sensitive than blood culture.
- E. The microbiology laboratory should be alerted regarding the suspected diagnosis.

Answer: E The microbiology laboratory should always be alerted in cases of suspected brucellosis. Aside from a potential biohazard, cultures may need to be kept longer than the usual incubation periods to increase yield. A single titer of 1 : 80 on STA is sufficient for a presumptive diagnosis in a nonendemic country. However, this person is from the Middle East, where *Brucella* is endemic, and this titer may represent previous exposure or infection. *B. canis* is not detected by the STA, and although the patient does have possible exposure from his three dogs, the STA would not be positive from this *Brucella* species. Blood culture sensitivity is about 30% and decreases with increasing duration of illness. Bone marrow culture is invasive but may be more sensitive than blood culture, especially in *B. melitensis* infection.

2. A 54-year old female veterinarian is admitted with a 1-week history of dyspnea and fever. Chest radiography shows cephalization and congestive changes with small bilateral pleural effusions. On examination, she has neck vein engorgement, fine bibasilar crackles, and a grade 4/6 systolic murmur. A transthoracic echocardiogram shows an 8-mm vegetation on the aortic valve. She is started on vancomycin 1 g intravenously every 12 hours, ceftriaxone 2 g intravenously every 24 hours, and diuretics with some improvement. Blood cultures grow *Brucella melitensis*. Which exposure is the most likely cause of this patient's brucellosis?

- A. Ingestion of unpasteurized goat cheese smuggled from Europe
- B. Assisting in the delivery of a stillborn calf
- C. A recent encounter with seals and sea lions at the local aquarium
- D. A visit to a pig farm to give vaccines
- E. A bite from a dog

Answer: A *B. melitensis* is acquired from goats, sheep, and camels, including unpasteurized dairy products from these animals. Bovine hosts transmit *B. abortus*, especially from spontaneously aborted fetuses. Seals and sea lions are possible sources of *B. pinnipedia*, pigs transmit *B. suis*, and dogs harbor *B. canis*.

3. The patient in question 2 continues to have shortness of breath and signs of congestion despite adequate diuresis. Then correct management for this patient is

- A. continue vancomycin but shift the ceftriaxone to ciprofloxacin and repeat transthoracic echocardiography in 6 weeks.
- B. continue vancomycin and ceftriaxone and refer to a cardiothoracic surgeon for early valve replacement.
- C. continue vancomycin but shift the ceftriaxone to ciprofloxacin and refer to a cardiothoracic surgeon for early valve replacement.
- D. stop vancomycin and ceftriaxone and start doxycycline and intramuscular streptomycin and refer to a cardiothoracic surgeon for early valve replacement.
- E. stop vancomycin and ceftriaxone and start doxycycline and intramuscular streptomycin and repeat echocardiogram in 6 weeks.

Answer: D The regimens of choice for *Brucella* infection include doxycycline in addition to either streptomycin or gentamicin. Early valve replacement has been shown to decrease mortality in *Brucella* endocarditis, so prompt referral to a cardiothoracic surgeon should be made. Vancomycin and ceftriaxone are not reliable alternative agents, and even though third-generation cephalosporins are used in alternative regimens, monotherapy is not recommended. Fluoroquinolones likewise have some activity against *Brucella* spp. but should not be used as monotherapy.

4. The intracellular nature of *Brucella* means that it must be able to avoid detection before entry into the cell and survive the defense mechanisms that the cell deploys to destroy pathogens. Which of the following statements is consistent with the strategy *Brucella* uses in its pathogenesis?

- A. *Brucella* has a modified lipopolysaccharide (LPS) that has substantially decreased activity against TLR9 but is still activated by complement.
- B. Pathogenic *Brucella* organisms are able to prevent acidification of the phagosome.
- C. Specific virulence factors such as the VirB type IV secretion system (T4SS) are induced with phagosome acidification, which enables the bacteria to survive both acidification and lysosome fusion.
- D. *Brucella* intercepts traffic between the nucleus and the ribosomes in order to replicate.
- E. Neutrophils are an integral part of the response against *Brucella*, and their absence leads to substantially depressed immune activation.

Answer: C Specific virulence factors such as T4SS are activated by phagosome acidification and enable *Brucella* to survive both acidification and lysosome fusion. Modified *Brucella* LPS has little activity against TLR4 and is resistant to complement activation. Acidification is an integral part of inducing T4SS, and *Brucella* does not inhibit this process. *Brucella* intercepts traffic between the endoplasmic reticulum and the Golgi apparatus, not between the nucleus and ribosomes. Neutrophils have been found to be inhibitory to the immune response toward *Brucella*, and absence of these cells leads to an enhanced response.

5. A 28-year-old farmer develops fever and severe hip pain over the past 3 weeks. Magnetic resonance imaging shows sacroiliitis, and his blood cultures grow gram-negative coccobacilli. The following measures could have been taken to decrease the risk of this disease EXCEPT

- A. wearing protective glasses and clothes when handling cattle and cattle products.
- B. pasteurization of cheese and dairy.
- C. eating only fully cooked meat.
- D. vaccination against the pathogen.
- E. vaccination of farm animals against the pathogen.

Answer: D There is currently no approved human vaccine against *Brucella* spp. All of the other choices are correct.

1. In the United States, persons most commonly acquire *F. tularensis* infection from

- A. mosquitoes.
- B. tick bites.
- C. skinning infected rabbits.
- D. person-to-person contact.
- E. both B and C.

Answer: E Mosquito bites are a common mode of acquisition of infection in Europe. Although highly infectious, tularemia is not spread from person to person.

2. Tularemia is considered a potential bioterrorism agent. Among characteristic(s) of the disease that merit its inclusion among threat agents, which one of the following is not true?

- A. *F. tularensis* produces an easily diagnosed illness.
- B. It is highly infectious.
- C. It can survive in the environment for long periods.
- D. It can be disseminated readily (e.g., by aerosol).
- E. A vaccine is not available.

Answer: A Indeed, because aerosol inoculation produces a nonspecific pneumonia that often defies quick diagnosis, many cases may occur before a bioterrorism event might be detected. This would have the advantage of disabling a large proportion of the target population rather quickly; the fear initiated by the recognition of the terrorism event would follow when the diagnosis became apparent.

3. It is thought that tularemic pneumonia may occur more commonly than is reported. Reasons for this include

- A. underreporting of diagnosed cases to public health authorities.
- B. physicians not eliciting exposure histories.
- C. omission of specific serologic diagnostic testing.
- D. empiric therapy of community-acquired pneumonia with fluoroquinolone antibiotics.
- E. all of the above.

Answer: E Because fluoroquinolones are active against *F. tularensis*, empiric treatment may cure some patients even though a specific diagnosis was not established.

1. A 45 year-old New York City police officer is brought to the emergency department (ED) with a 2-day history of fever to 104° F (40° C) and worsening cough, dyspnea, confusion, nausea, and vomiting. The patient is intubated emergently in the ED because of respiratory distress. Chest radiographs demonstrate dense lower lobe infiltrates bilaterally. Sputum is blood tinged; Gram staining reveals numerous gram-negative bacilli with faint bipolar staining.

Appropriate actions at this time include all of following except

- A. begin treatment with intravenous gentamicin and ciprofloxacin.
- B. obtain blood for culture and sensitivity testing.
- C. isolate the patient under airborne precautions.
- D. alert infection control, public health, and law enforcement officials.
- E. offer prophylaxis to ED personnel who intubated the patient.

Answer: C This scenario should raise serious concern for bioterrorism. Although naturally acquired infections can be treated with gentamicin alone, intentionally released strains may be engineered for resistance; therefore, use of multiple antimicrobials is advisable until sensitivities are known. Pneumonic plague is spread through droplets and can be prevented with droplet precautions; airborne precautions are unnecessary and likely to hinder patient care and management, especially if additional cases are identified. Although person-to-person transmission of plague has not been reported in the United States since 1925, unprotected close contact (<6 ft) is a risk factor, and prophylaxis with oral doxycycline is generally recommend.

2. A 34 year-old Los Angeles woman is hospitalized for fever and septic shock. On hospital day 2, admission blood cultures grow *Y. pestis*. On more careful reexamination, a large painful bubo is discovered in the patient's right axilla. The diagnosis of bubonic plague had not been suspected because the patient did not report traveling outside her urban Los Angeles neighborhood. Further interviews reveal that 3 days before illness onset, the patient had butchered a wild rabbit hunted by her husband and transported it to her home. In addition to handling tissues of infected wild animals, all of the following have been identified as risk factors for plague in the United States except

- A. living west of the 100th meridian.
- B. allowing dogs to sleep on the bed.
- C. contact with an ill cat.
- D. rodent die off in the area around the home.
- E. failure to use insect repellent.

Answer: E Plague is endemic in the western United States. For reasons not fully known, it has not been able to establish itself east of approximately the 100th meridian. Epidemiologic studies have identified allowing dogs to sleep on the bed as a risk factor, likely by increasing opportunities for exposure to infected fleas. Unlike dogs, which are relatively unaffected by plague, cats are highly susceptible and prone to infection through capture of rodents. Plague epizootics among rodents can lead to mass mortality and an abundance of infectious fleas seeking blood meals from other sources, including humans. Although it may be helpful, insect repellent has not been demonstrated to prevent human infection.

3. A previously healthy 55 year-old wildlife biologist presents to the emergency department in Santa Fe, New Mexico, with a 4-day history of fever, severe abdominal pain, and bloody stools. While being evaluated, the patient begins vomiting blood and develops acute respiratory distress. He is admitted but dies within a few hours. Two days later, blood cultures obtained at admission reveal an unidentified gram-negative rod. The isolate is sent to three different laboratories that use automated systems to identify the organism as *Acinetobacter lwoffii*, *Pseudomonas luteola*, and *Yersinia pseudotuberculosis*. The most likely explanation for this situation is

- A. laboratory contamination.
- B. the correct identification is *Y. pseudotuberculosis*.
- C. the correct identification is *P. luteola*.
- D. The correct identification is *A. lwoffii*.
- E. none of the above.

Answer: E Epidemiologic and clinical features are strongly suggestive of septicemic plague and not consistent with any of these other agents. Because of a lack robust biochemical profiles for *Y. pestis*, some automated microbiologic identification systems can misidentify the organism, usually as *Y. pseudotuberculosis*.

4. Which of the following regarding primary pneumonic plague is *false*?

- A. Can be acquired from infected cats
- B. Has not resulted in person-to-person transmission in North America since 1925
- C. Requires isolation of patients using droplet precautions
- D. Occurs in about 3% of patients with bubonic plague
- E. Is a likely presentation of an intentional release

Answer: D In North America, most cases of primary pneumonic plague are acquired from ill, infected cats. The last case of person-to-person transmission occurred in Los Angeles in 1925; however, cases acquired from cats continue to occur. Person-to-person transmission can be prevented with droplet precautions; airborne precautions are not necessary. Secondary, not primary, pneumonic plague occurs after bubonic plague. Although plague may be dispersed and acquired through various routes, an aerosol release resulting in primary pneumonic plague is considered the most likely and deadly.

5. Two previously healthy sibling boys, age 6 and 16 years, are brought to the clinic by their father. Both boys are complaining of fever (102° F) and abdominal pain. The 6-year-old boy reports diarrhea with bloody stools, verified by the father. The older boy denies diarrhea but has marked right lower quadrant abdominal pain with some rebound tenderness. When asked about dietary exposures, the father mentions that both boys had eaten poorly cooked pork at a winter solstice pig roast a few days earlier. Which of the following selective media is best for isolating the most likely cause of illness?

- A. Sorbitol MacConkey agar (SMAC)
- B. Xylose lysine deoxycholate agar (XLD)
- C. Cefsulodin–irgasan–novobiocin (CIN)
- D. Campylobacter blood agar plates (Campy-BAP)

Answer: C Although several pathogens can produce bloody diarrhea and abdominal pain, features of the scenario suggest infection with *Yersinia enterocolitica*. These include the association with undercooked pork, the mixed clinical features of bloody diarrhea in a younger child and pseudoappendicitis in an older child, and onset in winter. SMAC is the preferred media for isolating Shiga toxin *Escherichia coli* O157:H7, which classically cause bloody diarrhea with little or no fever. Both *Salmonella* and *Campylobacter* infections occur more often in the summer and fall, and both are generally associated with exposures to nonpork products, especially beef, eggs, produce, and poultry.

1. The leading or most logical explanation for the current resurgence of pertussis in the United States is
 - A. limited efficacy and duration of protection elicited by current acellular pertussis vaccines.
 - B. prolonged, asymptomatic carriage of *B. pertussis* after infection.
 - C. enhanced detection of *B. pertussis* with the use of polymerase chain reaction (PCR) technologies.
 - D. development of antibiotic resistance among circulating strains of *B. pertussis*.
 - E. adaptation of *B. pertussis* to selective pressure imposed by acellular vaccines containing only four or five protein antigens.

Answer: A The limited protection induced by acellular pertussis vaccines and the rapid decrease in that protection with time have been documented in numerous studies. Although animal recipients of acellular vaccine can become infected and transmit to other animals without developing signs, such as cough, there is no evidence for a prolonged carrier state such as that documented for other infectious diseases. The sensitivity of PCR for identification of *B. pertussis* is greater than that of classical methods such as culture. PCR has, however, been used for a number of years and cannot explain the striking increases observed from 2010 to 2012 and the current incidence in the United States, which is the highest in more than 50 years. Antibiotic resistance among *B. pertussis* strains has been reported but is rare and not clinically relevant at present. Finally, there is an increasing number of clinical isolates of *B. pertussis* that do not express pertactin, one of the antigens in the cellular vaccine, but these existed before use of acellular vaccines, and there is no evidence that they are appearing as a result of acellular vaccine use.

2. The characteristic paroxysmal cough associated with *B. pertussis* infection is caused by
 - A. tracheal cytotoxin (TCT).
 - B. pertussis toxin (PT).
 - C. filamentous hemagglutinin (FHA).
 - D. pertactin (PRN).
 - E. none of the above.

Answer: E Although it has been speculated that several of the listed virulence factors could be responsible for the cough of whooping cough, none of these molecules alone can cause the cough in experimental animals (or, in some cases, in humans). It is unknown how infection with *B. pertussis* results in paroxysmal cough associated with whooping.

1. All of the following are risk factors for legionnaires' disease, except
 - A. Cigarette smoking
 - B. Travel to Europe
 - C. Treatment with anti-tumor necrosis factor
 - D. Using potting soil for your garden in Australia
 - E. Being a member of the American Legion

Answer: E The disease was first recognized during a convention by the American Legion and was caused by water contamination with the organism at the hotel in Philadelphia that served as the meeting headquarters, not by any host factors. All of the other factors have been shown in one or more studies to increase one's risk of acquiring legionnaires' disease.

2. You have just seen a 55-year-old man with right lower lobe pneumonia. He has been receiving dialysis three times per week at an outpatient facility. He is quite ill, and you are concerned that he might have legionnaires' disease. The result of the *Legionella* urinary antigen test that you ordered is negative. Which of the following is correct?

- A. Your patient does not have legionnaires' disease.
- B. Your patient may still have legionnaires' disease.
- C. Serologic testing will confirm the diagnosis.
- D. Blood cultures will be positive for *Legionella*.
- E. Sputum culture is a good test for *Legionella*.

Answer: B The urine antigen test detects only infection due to *L. pneumophila* serogroup 1, and even then it is only 74% sensitive. So your patient could still have legionnaires' disease, either serogroup 1 or another *Legionella* species. Sputum culture, if positive, is 100% specific. Unfortunately, most patients with legionnaires' disease do not produce sputum, and even more problematic is the fact that many laboratories are unable to grow this microorganism. Serologic diagnosis takes 4 to 6 weeks, so it is not of any use in therapeutic decision making. Also, the sensitivity can be low, especially in patients with an impaired immune response.

3. A patient has developed legionnaires' disease while hospitalized for treatment of acute pancreatitis. He spent 3 weeks in intensive care and had a nasogastric tube in place for most of that time. What was the most likely source of the patient's *Legionella*?

- A. He acquired it before admission.
- B. His daughter, who lives in Athens, came to visit him. She was coughing frequently during her many visits.
- C. The air conditioning system
- D. The potable water

Answer: D In all likelihood, the potable water is the source. You should check the protocol for nasogastric tubes in your hospital. Not uncommonly, potable water is used to initiate feeding. If the potable water is contaminated with *Legionella*, it is readily aspirated into the lungs in patients who are in a recumbent position in an intensive care unit. Person-to-person transmission of *Legionella* has not been documented. If the air conditioning system was contaminated, it would likely be through a cooling tower, and there would have likely been an outbreak of many cases of *Legionella*. Whereas it is always possible that *Legionella* was acquired before admission, the incubation period for legionnaires' disease is 2 to 10 days. It is possible to have a much longer incubation period. In the event of other cases in the hospital, molecular biology typing techniques can be used to identify the organism as coming from the potable water.

4. The following are extrapulmonary manifestations of legionnaires' disease.

- A. Prosthetic valve endocarditis
- B. Cerebellar ataxia
- C. Reactive arthritis
- D. Oral ulcers
- E. A, B, and C

Answer: E Prosthetic valve endocarditis is due to direct infection of the valve by circulating *Legionella* bacteria. Cerebellar ataxia and reactive arthritis represent immunologic reactions in these tissues and are not due to direct infection.

5. The treatment of choice for moderate to severe legionnaires' disease is

- A. Erythromycin
- B. Amoxicillin
- C. Levofloxacin
- D. Vancomycin
- E. Ceftriaxone

Answer: C A respiratory fluoroquinolone is probably the best antibiotic class for treatment of moderate to severe legionnaires' disease. There are not data from randomized clinical trials to provide guidance in this regard. Our recommendations are from observational studies. We do know that β -lactams are ineffective and erythromycin, although initially used to treat legionnaires' disease, takes 4 to 5 days to show improvement. Indeed, most patients get worse before they get better after treatment with erythromycin. Vancomycin would not be expected to work on a microorganism with a gram-negative cell wall.

Ch / 315 **BARTONELLA INFECTIONS**

1. Which of the following is the main vector of *Bartonella quintana* infections in humans?

- A. Mites
- B. Lice
- C. Ticks
- D. Bed bugs
- E. Fleas

Answer: B The human body louse is the main vector (see Table 315-1), but *B. quintana* could be detected in fleas and ticks.

2. Which treatment is the most appropriate recommendation for *Bartonella* endocarditis?

- A. Erythromycin
- B. Doxycycline plus rifampin
- C. Doxycycline
- D. Doxycycline plus gentamicin
- E. Streptomycin

Answer: D *Bartonella* endocarditis should be treated with doxycycline for 6 weeks plus gentamicin for 14 days. (See Treatment section.)

3. Which laboratory method is the most appropriate for the diagnosis of cat-scratch disease (CSD)?

- A. Real-time polymerase chain reaction
- B. Serology
- C. Gram staining
- D. Cell culture
- E. Immunohistochemistry

Answer: A Serology remains a widely used method where molecular methods are not available for the diagnosis of CSD and *Bartonella* endocarditis because culture and isolation are difficult and time-consuming. However, the reported sensitivities of immunofluorescence assays vary considerably, depending on the nature of the antigen used and the selected patients. Furthermore, because of cross-reactivity of antibodies between *Bartonella* species, serologic methods usually cannot make the diagnosis of *Bartonella* infection at the species level. Direct detection and definitive *Bartonella* species identification are possible from blood and tissue (e.g., lymph node) specimens. See Table 315-3.

4. Which *Bartonella* species is the causative agent of peliosis hepatis?

- A. *B. quintana*
- B. *B. henselae*
- C. *B. bacilliformis*
- D. *B. grahamii*
- E. *B. alsatica*

Answer: B Peliosis hepatis is characterized by the development of cystic, blood-filled cavities throughout the liver parenchyma and can be caused by a variety of drugs, malignant neoplasms, post-renal transplantation, and different infections including human immunodeficiency virus infection, tuberculosis, and *Bartonella henselae*.

5. Which treatment is the most appropriate recommendation for bacillary angiomatosis?

- A. Erythromycin
- B. Doxycycline plus rifampin
- C. Doxycycline
- D. Doxycycline plus gentamicin
- E. Streptomycin

Answer: A Erythromycin (500 mg four times daily) for 3 months is first-line therapy. (See Treatment section.)

Ch / 316 GRANULOMA INGUINALE (DONOVANOSIS)

1. Which of the following statements regarding granuloma inguinale is correct?

- A. It is transmitted efficiently and only by sexual contact.
- B. The initial lesion is typically painful and associated with fever.
- C. Lesions are associated with buboes.
- D. Diagnosis requires demonstration of intracellular Donovan's bodies.
- E. Diagnosis requires serologic confirmation.

Answer: D No serologic test is clinically available for granuloma inguinale, and definitive diagnosis depends on demonstration of Donovan's bodies in mononuclear cells from lesion scrapings or biopsy samples. Although it is primarily transmitted through sexual contact, the organism can probably be transmitted by nonsexual contact as well; transmission efficiency is low. The lesion is painless, and it is not accompanied by systemic symptoms. It is associated with a so-called pseudobubo, a swelling in the inguinal area caused by granulomatous infiltration of subcutaneous tissue—not actual inguinal lymph node involvement that would constitute a bubo.

Ch / 317 MYCOPLASMA INFECTIONS

1. *Mycoplasma pneumoniae* is one of the most common causes of the atypical pneumonia syndrome. Another organism that shares many of the characteristics of organisms causing this syndrome is

- A. *Streptococcus pneumoniae*
- B. *Chlamydophila pneumoniae*
- C. *Staphylococcus aureus*
- D. *Klebsiella pneumoniae*
- E. *Acinetobacter baumannii*

Answer: B *Chlamydophila* does not show up on Gram stain or grow in common bacterial culture, two of the common characteristics of these “atypical” organisms. (See Definition section.)

2. Which of the following classes of antimicrobials would *not* be effective in treating pneumonia in a young adult caused by *M. pneumoniae*?

- A. Fluoroquinolones
- B. β -Lactamase-resistant penicillins
- C. Extended-spectrum macrolides
- D. Tetracyclines
- E. MLSK class

Answer: B Mycoplasmas do not have cell walls, and the penicillins work by inhibiting cell wall synthesis. The other drugs all are effective in treating *M. pneumoniae*. (See section on treatment.)

3. Which of the following is true of cold agglutinins that occur in about 50 to 70% of patients with *M. pneumoniae* pneumonias?

- A. They are IgG antibodies directed against the nucleic acid of the organism.
- B. They are secreted by the organism as part of the infectious process.
- C. They help to neutralize the organism and thereby protect the host.
- D. They are IgM class antibodies directed at antigens on the host erythrocyte.
- E. When present, they are pathognomonic of *Mycoplasma* infection.

Answer: D Mycoplasma-induced cold agglutinins are IgM antibodies directed at the I antigens of red cell membranes. They are detected by a positive direct antiglobulin test (DAT) result, also known as the direct Coombs' test. Although clinically significant hemolysis is rare, subclinical positivity for DAT is common in *Mycoplasma* pneumonia. (See Pathobiology section.)

4. Which of the following is true about *Mycoplasma hominis*?

- A. Causes puerperal sepsis
- B. Is sensitive to macrolides, as are the other mycoplasmas
- C. Is a common cause of infectious carditis
- D. Is the most common cause of nonbacterial urinary tract infection
- E. Has, as its primary reservoir in nature, the feral cat

Answer: A *M. hominis* is a common genitourinary and oral commensal, but it has also been documented as a cause of endometritis and postpartum fever. (See section on epidemiology.)

5. Which of the following chest radiographic patterns would be most characteristic of *M. pneumoniae* pneumonia?

- A. Pneumothorax
- B. Dense, multilobar alveolar infiltrates
- C. Dense unilobar infiltrate with ipsilateral pleural effusion
- D. No infiltrate seen
- E. Multifocal interstitial pattern

Answer: E The disparity between the paucity of physical findings and the radiographic appearance of pneumonia in this condition can be striking (see Fig. 317-2).

1. Which of the following is *not* a recommended strategy for the elimination of trachoma and its complications?

- A. Surgery to correct trichiasis
- B. Mass antibiotic treatments within a trachoma-endemic community
- C. Face washing and good hygiene
- D. Achieving better sanitary conditions in the environment
- E. Education to promote safer sexual practices

Answer: E The World Health Organization is committed to the elimination of trachoma and its complications by 2020 and recommends that endemic countries adopt the SAFE strategy: surgery (for trichiasis), antimicrobials (periodic community-wide treatment), facial cleanliness, and environmental sanitation improvement. Trachoma is spread by direct contact with fingers or fomites (e.g., washcloths, handkerchiefs) contaminated with eye discharge from an infected person or by eye-seeking flies, not through sexual transmission.

2. Routine annual screening for genital chlamydial infection is recommended by the Centers for Disease Control and Prevention (CDC) for the following patient group:

- A. All sexually active women
- B. All sexually active men
- C. Sexually active women 25 years of age and younger
- D. Sexually active men 25 years of age and younger
- E. None of the above

Answer: C Routine genital chlamydia screening (i.e., testing of asymptomatic persons for chlamydia) in women has been shown to reduce the rate of pelvic inflammatory disease. Surveillance data from the CDC have shown that the majority of chlamydia cases reported each year are in women 25 years of age and younger. Therefore, the CDC recommends routine annual screening for genital chlamydial infection in women within this age group. Screening in women older than 25 years of age is recommended only if risk factors (e.g., new sexual partner, multiple sexual partners) are present. Routine chlamydia screening is not recommended for men; however, screening should be considered for men in venues with a high prevalence of chlamydia (e.g., STD clinics).

3. The recommended treatment for lymphogranuloma venereum (LGV) infection is

- A. Doxycycline 100 mg twice daily orally for 7 days
- B. Doxycycline 100 mg twice daily orally for 21 days
- C. Azithromycin 1 g orally single-dose therapy
- D. Erythromycin 500 mg four times a day for 21 days
- E. Ciprofloxacin 500 mg twice daily for 7 days

Answer: B *Chlamydia trachomatis* strains of the LGV serovar/genotype cause more invasive disease than the non-LGV strains do, and therefore a course of doxycycline 100 mg twice daily for 21 days is recommended. There is insufficient clinical experience with macrolides to recommend them as a first-line agent for LGV. Some experts do recommend azithromycin 1 g weekly for 3 weeks as an alternative to the 3-week doxycycline regimen, but a single dose of azithromycin is believed to be insufficient to reliably cure invasive LGV infections. Ciprofloxacin has poor in vitro activity against *C. trachomatis* and is not recommended for treatment of LGV or non-LGV *C. trachomatis* infections.

4. Which of the following statements regarding *Chlamydia pneumoniae* is most accurate?
- A. The seroprevalence of *C. pneumoniae* in adults in the United States is estimated to be around 15%.
 - B. Pneumonia caused by *C. pneumoniae* usually is manifested as an acute-onset illness with cough productive of purulent sputum.
 - C. *C. pneumoniae* causes upper respiratory tract infections, including pharyngitis and bronchitis.
 - D. Penicillin is a highly effective treatment for *C. pneumoniae* respiratory infections.
 - E. Large clinical trials have consistently demonstrated a reduction in adverse cardiovascular events in patients receiving antibiotic treatment directed against *C. pneumoniae*.

Answer: C The majority of adults in the United States and other developed nations are seropositive for *C. pneumoniae*. It is well known that *C. pneumoniae* can cause upper and lower respiratory tract infections. Pneumonia caused by *C. pneumoniae* usually develops gradually with a nonproductive cough, referred to as a walking pneumonia, in contrast to pneumococcal pneumonia, which is more likely to be acute in onset with a productive cough. *C. pneumoniae* respiratory infections are most effectively treated with an antibiotic from the tetracycline, macrolide, or respiratory fluoroquinolone (levofloxacin, moxifloxacin) class and are not adequately treated by a β -lactam antibiotic such as penicillin. Even though *C. pneumoniae* has been associated with atherosclerosis, large *C. pneumoniae* treatment trials have not demonstrated benefit in preventing adverse cardiovascular events.

5. Which of the following statements regarding *Chlamydia psittaci* is *not* true?
- A. *C. psittaci* infection has been associated with exposure to psittacine birds (parrots, parakeets, and budgerigars).
 - B. *C. psittaci* infection has been associated with exposure to turkeys.
 - C. Birds may be carriers of *C. psittaci* but do not develop clinical disease.
 - D. *C. psittaci* infection can be manifested as an abrupt-onset febrile illness in humans.
 - E. *C. psittaci* has been classified as a biocontainment level 3 agent.

Answer: C *C. psittaci* infection has been associated with exposure to psittacine birds and several other nonpsittacine birds, including turkeys. Whereas birds may be asymptomatic carriers of *C. psittaci*, they may also develop a mild symptomatic illness manifested by ruffled feathers, anorexia, shivering, dyspnea, diarrhea, or depression. *C. psittaci* infection can be manifested as an abrupt-onset febrile illness in humans with pulmonary and extrapulmonary manifestations. *C. psittaci* has been classified as a biocontainment level 3 agent because of its stability in the environment and aerosol transmission. Because laboratory-acquired *C. psittaci* infections are well documented, culture is discouraged and serology is preferred for diagnosis.

Ch / 319 SYPHILIS

1. A 33-year-old man is referred to you after receipt of notification that a blood test result for syphilis performed at the time of a recent blood donation was positive. You learn that the test was a treponemal enzyme immunoassay (EIA). A rapid plasma reagin (RPR) test performed in follow-up was nonreactive. He reports being in a long-standing, mutually monogamous sexual relationship. Physical examination shows no evidence of syphilis. Possible explanations for his reactive EIA and nonreactive RPR syphilis test results are
- A. Residual antibody reactivity after successful treatment of syphilis in the past
 - B. Previously undetected latent syphilis of unknown duration
 - C. A falsely positive test result
 - D. He has acquired syphilis so recently that his RPR test result is not yet positive
 - E. All of the above

Answer: E Results of recently developed treponemal antigen EIA tests for syphilis are not uncommonly positive while results of nontreponemal tests, such as the RPR and Venereal Disease Research

Laboratory (VDRL) tests, are negative. In most settings (and in this patient), unless there is a history of prior treated syphilis, this typically reflects a falsely positive test result; more uncommonly, it could represent previously undetected latent syphilis or, very rarely, recently acquired syphilis before the development of a reactive RPR or VDRL test result (lesions of primary syphilis are typically present in these situations).

2. You are asked to recommend management for a 27-year-old woman with secondary syphilis who is midway through her second trimester of pregnancy. The patient has a well-documented history of penicillin allergy. The recommended therapy for this patient is

- A. Doxycycline 100 mg twice daily for 14 days
- B. Azithromycin 2.0 g orally as a single dose
- C. Ceftriaxone 500 mg IM or IV once daily for 10 days
- D. Penicillin desensitization followed by a single intramuscular injection of 2.4 million units of benzathine penicillin
- E. Penicillin desensitization followed by two intramuscular injections of 2.4 million units of benzathine penicillin administered a week apart

Answer: D For treatment of syphilis in pregnancy, there are no recommended alternatives to penicillin for therapy. Doxycycline could cause dental staining in her child, and neither doxycycline nor azithromycin has been studied in this situation. As a result, pregnant, penicillin-allergic patients should be desensitized and treated as recommended for the stage of disease they have. There is no evidence that pregnant patients need treatment with higher doses or prolonged therapy.

3. In 2013, early syphilis was most common among minority groups and particularly common among

- A. Persons who use illicit drugs, such as cocaine or heroin
- B. Men who have sex with other men
- C. Adolescents
- D. Commercial sex workers
- E. Heterosexuals in monogamous relationships

Answer: B During the past 50 years, the epidemiology of syphilis has periodically shifted. Following an epidemic of syphilis in heterosexual men and women in the 1990s associated with a contemporary epidemic of crack cocaine use, the epidemiology of early syphilis again shifted. Since the beginning of the 21st century, syphilis in the United States has disproportionately occurred among men who have sex with men, including those infected with human immunodeficiency virus (HIV). As a result, annual (or more frequent, depending on sexual history) screening for syphilis is recommended for men who have sex with men and all persons with HIV infection.

4. A 34-year-old man with HIV infection well controlled by antiviral therapy presents with the acute onset of right-sided weakness. His CD4 lymphocyte count is 540/mm³. In the course of his evaluation, he is found to have reactive RPR (positive at a 1 : 64 dilution) and *T. pallidum* particle agglutination (TP-PA) test results. Lumbar puncture reveals the following cerebrospinal fluid (CSF) findings: cell count, 32 cells (100% mononuclear); protein level, 54 mg/dL; glucose concentration, 63 mg/dL (simultaneous serum glucose concentration, 10 mg/dL); and a nonreactive CSF VDRL test response. The most likely diagnosis in this man is

- A. Latent syphilis with CSF abnormalities attributable to his HIV infection
- B. Meningovascular syphilis
- C. Embolic stroke
- D. Hypertensive stroke

Answer: B This patient is a member of a group at risk for acquisition of syphilis (HIV-infected men who have sex with other men), is relatively young to have atherosclerotic stroke, and has CSF abnormalities consistent with neurosyphilis. His RPR test result is consistent with active syphilis. The

CSF VDRL test response is reactive in less than 70% of persons with neurosyphilis and need not be present for diagnosis of neurosyphilis. Whereas HIV infection can lead to elevations of CSF mononuclear cells, this rarely exceeds 20 cells unless other pathologic processes are present. Although other possibilities for stroke in relatively young persons should be considered, the most likely diagnosis in this man is meningovascular neurosyphilis.

5. A patient presents to you reporting that he was just notified that a casual sex partner he had sex with about 6 months ago was diagnosed with secondary syphilis shortly afterward. His exposures included multiple episodes of genital and oral intercourse. On physical examination, there is no clinical evidence of syphilis. At this point, in addition to serologic testing for syphilis, recommended management is

- A. Preventive treatment with intramuscular injections of 2.4 million units of benzathine penicillin G
- B. Serologic testing at this time and again 6 months in the future (treatment based on serologic test results)
- C. Serologic testing at this time; no subsequent testing is needed (treatment based on serologic test results)
- D. Reassurance that based on the fact that there is no history of lesions and his negative test results, there is no reason for concern and no further follow-up or treatment is needed

Answer: C Because lesions of syphilis may be painless and subtle, serologic testing is recommended for all persons reporting exposure to a partner with syphilis. Preventive penicillin is recommended treatment for persons exposed to sex partners within the preceding 90 days. In this patient, the exposure was 6 months ago, so only serologic testing is recommended. There is no need for treatment if the serologic test result for syphilis is negative and no need for testing beyond this time.

1. Nonsyphilitic treponematoses can be differentiated from syphilis by

- A. Serologic testing
- B. Response to therapy
- C. Clinical and epidemiologic characteristics
- D. Dark-field microscopy

Answer: C Traditionally, the human treponematoses have been differentiated on the basis of their clinical manifestations and epidemiologic characteristics because the etiologic agents are indistinguishable in the laboratory. They all respond to penicillin therapy.

2. The clinical course of untreated nonsyphilitic treponematoses is characterized by

- A. Lesions at the site of inoculation that resolve without therapy
- B. Risk for congenital transmission
- C. Risk for central nervous system disease
- D. Uniform progression to chronic, deforming disease in all untreated persons

Answer: A Unlike syphilis, the nonsyphilitic treponematoses are not transmitted across the placenta and do not invade the central nervous system to cause clinical disease. Only a proportion of individuals with long-standing untreated infection are at risk for late sequelae like bone deformities, nasal cartilage destruction, or chronic skin changes.

1. Aside from the egg, there are three feeding stages of the deer tick, *Ixodes scapularis*: the larval, nymphal, and adult stages. Adult deer ticks have higher infection rates with *Borrelia burgdorferi* than the other stages do. Which stage is the most important epidemiologically for transmission of *B. burgdorferi* to humans?

- A. Egg
- B. Larval
- C. Nymphal
- D. Adult
- E. Egg and larval stages

Answer: C The nymphal stage is the most important epidemiologically for transmission of infection to humans. The larval stage, which is the first stage, is uninfected and cannot transmit the infection. The adult stage, which is the third stage, is infected with *B. burgdorferi*, but it is less important in transmission to humans because this stage is present in smaller numbers in the environment. (See Epidemiology section.)

2. A single 200-mg dose of doxycycline should be considered to prevent Lyme disease under which circumstance?

- A. Documented *I. scapularis* tick bite in which the tick had been attached for 36 hours or more and doxycycline can be given within 72 hours after tick removal
- B. Clinical suspicion of a tick bite based on the presence of a scab on the leg
- C. Any documented *I. scapularis* tick bite regardless of duration of attachment
- D. Any documented tick bite
- E. In patients with suspected erythema migrans

Answer: A Doxycycline is particularly effective for prevention of Lyme disease when there has been a documented *I. scapularis* tick bite in an area highly endemic for Lyme disease in which the tick had been attached for 36 hours or more and doxycycline can be given within 72 hours after tick removal. (See Epidemiology and Prevention sections.)

3. Which of the following would be least consistent with early or late neurologic Lyme disease?

- A. Cerebrospinal fluid (CSF) with 150 white cells, 95% lymphocytes
- B. Peripheral unilateral seventh nerve palsy with an 8 × 10-cm erythematous skin lesion on the right thigh
- C. Bilateral peripheral seventh nerve palsies
- D. CSF with 1000 white cells, 85% polymorphonuclear leukocytes
- E. Six months of chronic headache with CSF showing 35 white cells, 95% mononuclear cells; test result for intrathecal production of antibody to *B. burgdorferi* is positive, and IgG antibody to *B. burgdorferi* is present in serum

Answer: D Neither early nor late neurologic Lyme disease is associated with a neutrophilic pleocytosis in the CSF. (See Clinical Manifestations section.)

4. Serologic testing to support a diagnosis of Lyme disease is usually not recommended in patients with possible

- A. Erythema migrans
- B. Lyme arthritis
- C. Early neurologic Lyme disease
- D. Lyme carditis
- E. Late neurologic Lyme disease

Answer: A Because of the short duration of infection at the erythema migrans stage, serologic assays for antibodies to *Lyme borrelia* are rarely positive when this finding is noted. (See Diagnosis section.)

5. Which of the following antimicrobials is ineffective for Lyme disease?

- A. Doxycycline
- B. Ceftriaxone (third-generation cephalosporin)
- C. Cefuroxime (second-generation cephalosporin)
- D. Amoxicillin
- E. Cephalexin (first-generation cephalosporin)

Answer: E *B. burgdorferi* is resistant to first-generation cephalosporins as well as to certain fluoroquinolones and rifampin. (See Treatment section.)

1. The differential diagnosis for a patient presenting with an undifferentiated febrile illness, chills, headache, and recent tick exposure include **all but one** of the following:

- A. Lyme disease
- B. Rocky Mountain spotted fever (RMSF)
- C. Ehrlichiosis
- D. Tick paralysis
- E. Anaplasmosis

Answer: D Not tick paralysis, which is not an infection but in fact an intoxication due to a tick neurotoxin. An undifferentiated febrile illness with recent tick exposure could include Lyme disease, RMSF, ehrlichiosis, and anaplasmosis.

2. Causes of a peripheral facial nerve palsy include **all but one** of the following:

- A. Lyme disease
- B. Herpes simplex virus (HSV)
- C. Sarcoidosis
- D. Babesiosis
- E. Relapsing fever

Answer: D Not babesiosis. HSV is the most likely cause of Bell's palsy, with the borrelial infections, Lyme disease, and relapsing fever not uncommon, and sarcoidosis rare.

3. Diagnosis of relapsing fever can include **all but one** of the following:

- A. Serology (acute and convalescent)
- B. Positive blood smear for a spirochete
- C. Polymerase chain reaction (PCR) assay of blood
- D. Sleeping in rustic cabins in the U.S. West
- E. Blood cultures

Answer: E Blood cultures cannot culture the *Borrelia* bacteria that cause relapsing fever; however, the number of organisms per milliliter of blood is so high they can be seen on a blood smear and detected by PCR.

4. Treatment of relapsing fever is:

- A. Tetracycline
- B. Ceftriaxone
- C. Complicated by Jarisch-Herxheimer reaction
- D. A and B
- E. A, B, C

Answer: E Tetracycline and ceftriaxone are equally effective, and either can cause the Jarisch-Herxheimer reaction.

5. Complications of relapsing fever include:

- A. Jarisch-Herxheimer reaction
- B. Meningitis
- C. Jaundice
- D. A and C
- E. All of the above

Answer: E Relapsing fever can be complicated by meningitis, jaundice (especially the louse-borne form), and the Jarisch-Herxheimer reaction, which is treatment associated and probably due to accelerated phagocytosis of spirochetes by neutrophils and the consequent elevation in levels of tumor necrosis factor (TNF)- α and interleukin (IL)-6, IL-8, and IL-10.

Ch / 323 LEPTOSPIROSIS

1. Which group is least at risk for leptospirosis?

- A. Hospital workers
- B. Veterinarians
- C. Farmers
- D. Sewage workers
- E. Urban homeless

Answer: A Health care workers are at low risk for leptospirosis because human-to-human transmission is rare and primarily involves vertical transmission from mother to infant. Because *Leptospira* species are zoonoses that can persist in the environment, persons with exposure to domestic or wild animals, soil, or fresh water are at greatest risk. The urban poor of both temperate and tropical climates are an underappreciated population at risk.

2. Which is the least likely presentation of leptospirosis?

- A. High fever and headache
- B. Aseptic meningitis
- C. Cough and hemoptysis
- D. Localized seizure
- E. Acute cholecystitis

Answer: D Localized seizure would be an atypical presentation of leptospirosis, which is generally not considered to be associated with focal neurologic findings. Hemoptysis and renal and hepatic failure are classic presentations of severe leptospirosis. Fever is very common, and aseptic meningitis is well described. Leptospirosis can be associated with acute abdominal pain, and acute cholecystitis has been described as a disease presentation.

3. What is the most likely renal finding in leptospirosis?

- A. Cortical necrosis
- B. Massive proteinuria
- C. Hyperkalemic nonoliguric renal failure
- D. Pyelonephritis
- E. Allergic nephritis

Answer: C Hyperkalemic nonoliguric renal failure is the typical renal presentation of leptospirosis, which can progress to oliguric renal failure. Hypokalemia is an important laboratory value that can support the diagnosis of leptospirosis. Treatment involves volume resuscitation to prevent oliguric renal failure, electrolyte replacement, and prompt consideration of dialysis. Massive proteinuria would be atypical and suggests a different etiology. The pathologic findings are of interstitial nephritis; cortical necrosis, pyelonephritis, and eosinophilic infiltrates are typically not seen.

4. Of the following, what is the most likely clinical presentation and associated finding in leptospirosis?

- A. Jaundice with markedly elevated transaminases
- B. Myalgia with elevated creatine kinase
- C. Petechiae and markedly prolonged prothrombin time
- D. Fever and pancytopenia
- E. Severe headache and papilledema

Answer: B Myalgia in leptospirosis is associated with elevated creatine kinase. Myalgia can be extremely painful and mimic an acute abdomen or the nuchal rigidity seen in meningitis. Jaundice is classically seen in leptospirosis, but transaminases are generally low despite markedly elevated bilirubin; these findings can be an important clue to support the diagnosis of leptospirosis. Petechiae and a bleeding diatheses, including massive pulmonary hemorrhage, can be present, but coagulation parameters are typically not markedly abnormal. Fever and headache are very common, but pancytopenia and papilledema would be unusual.

5. Of the following, which are the most likely pathologic findings in leptospirosis?

- A. Massive hepatic necrosis and acute renal tubular injury
- B. Pulmonary hemorrhage, interstitial nephritis, and hepatocellular dissociation
- C. Neutrophilic bronchopneumonia and interstitial nephritis
- D. Vasculitis with abundant intravascular spirochetes
- E. Pulmonary and renal infarction

Answer: B Massive pulmonary hemorrhage, interstitial nephritis, and hepatocellular dissociation are the typical findings seen at autopsy. Massive hepatic necrosis is generally not seen and would suggest dengue or yellow fever virus infection (depending on the geographic location) or other causes of acute fulminant liver failure. Leptospiral organisms do not cause neutrophilic bronchopneumonia. Vasculitis is generally not a prominent feature of leptospirosis, although a degree of inflammation has been described within pulmonary vessel walls. *Leptospira* species spirochetes are not intravascular but associated with the interstitium; these organisms have several well-defined mechanisms to bind collagen and other components of the extracellular matrix. Infarcts are not a typical feature and would suggest a thromboembolic process.

1. The following is true of tuberculosis (TB) in the United States:

- A. Most cases are in the foreign born.
- B. Most cases are in the HIV infected.
- C. The elderly are not at risk.
- D. The period of greatest risk of progression is 5 years and longer after infection.
- E. Outbreaks are a major source of multidrug-resistant (MDR) TB cases.

Answer: A Foreign-born individuals account for over 60% of U.S. TB cases. The greatest risk of progressing to disease is in the first and second years after infection. Outbreaks have been limited by application of infection control measures.

2. Advantages of interferon gamma release assays (IGRAs) such as Quantiferon-Gold for the diagnosis of latent TB infection include all the following **except**:

- A. More specific than tuberculin skin test (TST)
- B. Reproducible results in health care workers
- C. Does not require return visits
- D. End points are objective.
- E. Antigens are not found in BCG.

Answer: B There is lack of reproducibility in serial testing, particularly if the “positive” is close to end point.

3. The advantages of GenXpert MTB/RIF for the diagnosis of TB include all the following **except**:

- A. Useful in monitoring therapy
- B. More sensitive than smear
- C. Does not require proficiency in molecular technology
- D. More rapid than culture
- E. Provides rifampin susceptibility

Answer: A Not useful in monitoring therapy; the presence of *Mycobacterium tuberculosis* DNA in sputum does not indicate that there are viable organisms.

4. Which of the following is true concerning treatment of MDR TB:

- A. The strategy of adding a single drug to retreatment regimens is cost-effective.
- B. Empirical therapy is as good as tailoring regimen to drug susceptibility.
- C. Acquisition of additional drug resistance is unlikely.
- D. Standard duration of therapy (6 months) is adequate.
- E. New drugs with potent activity now are available.

Answer: E Bedaquiline and delamanid have been approved by the FDA. Adding a single drug to a retreatment regimen is inadequate in one fourth of cases.

5. Which of the following is true regarding treatment of latent TB infection (LTBI)?

- A. There is a prolonged effect in HIV-infected persons.
- B. A 12-dose regimen of rifapentine-isoniazid is effective.
- C. Treatment requires both a positive TST and IGRA.
- D. There is no need to monitor for adverse events.
- E. Screening in HIV-infected patients in resource-limited settings requires chest x-ray and culture.

Answer: B A 12-dose course of rifapentine-isoniazid is effective. The efficacy of isoniazid preventive therapy in HIV-infected patients in high-transmission settings wanes after 6 to 12 months.

1. Initial *Mycobacterium avium* complex (MAC) susceptibility testing is recommended and validated for which of the following?

- A. Rifamycins
- B. Macrolides
- C. Aminoglycosides
- D. Ethambutol
- E. All of the above

Answer: B The only antibiotic class for which there is evidence for in vitro testing to predict in vivo value is macrolides. The other agents have limited predictive value in in vitro testing for MAC. Therefore, only macrolide testing is recommended and interpretable with break points.

2. Pulmonary MAC infection is associated with which of the following underlying conditions?

- A. Cystic fibrosis
- B. Primary ciliary dyskinesia
- C. Bronchiectasis
- D. Pneumoconiosis
- E. All of the above

Answer: E Isolated pulmonary MAC infection has been clearly associated with defects in respiratory ciliary function and channel defects affecting the respiratory epithelium.

3. Disseminated MAC infection is associated with which of the following conditions?

- A. Mutations in the interleukin (IL)-12 receptor
- B. Mutations in the interferon (IFN)- γ receptor
- C. Mutations in *STAT1*
- D. Tumor necrosis factor (TNF)-inhibiting antibodies
- E. All of the above

Answer: E The IL-12/IFN- γ pathway is critical for the control of intracellular organisms including nontuberculous mycobacteria. IFN- γ also induces TNF- α , linking these two pathways together.

4. Nontuberculous mycobacteria (NTM) are relatively ubiquitous in the environment. Which organism is the most common cause of nontuberculous mycobacterial infection in humans?

- A. *Mycobacterium gordonae*
- B. *Mycobacterium smegmatis*
- C. MAC
- D. *Mycobacterium abscessus* complex
- E. *Mycobacterium kansasii*

Answer: C MAC is a compilation of *M. avium*, *M. intracellulare*, and *M. avium* X-cluster. The leading cause of disseminated NTM infection is *M. avium*, whereas the majority of isolated pulmonary NTM is due to *M. intracellulare*. *M. avium* X-cluster is a relatively infrequent cause of disease that is usually extrapulmonary.

5. Nontuberculous mycobacterial osteomyelitis is rare outside of genetic immunodeficiency. Which immunodeficiency is it most associated with?

- A. Chronic granulomatous disease
- B. Anti-TNF antibody therapy
- C. Recessive deficiency of IFN- γ R
- D. Dominant negative deficiency of IFN- γ R
- E. Advanced HIV

Answer: D Osteomyelitis due to NTM and bacille Calmette Guérin (BCG) is strongly associated with the autosomal dominant form of IFN- γ receptor 1 deficiency. Isolated osteomyelitis due to NTM is much less common in the recessive forms of IFN- γ receptor 1 deficiency and very unusual in other genetic defects.

Ch / 326 **LEPROSY (HANSEN DISEASE)**

1. A 23-year-old Brazilian man was seen by a dermatologist for evaluation of multiple bilateral plaques and nodules; biopsy revealed poorly formed granulomas with multiple foamy cells, and Fite stain revealed multiple acid-fast bacteria. Additional investigation revealed glucose-6-phosphate dehydrogenase (G6PD) deficiency with the Mediterranean variant. What are the potential treatment options for this patient's leprosy?

- A. Rifampin and dapsone
- B. Rifampin and clarithromycin
- C. Rifampin
- D. Rifampin and clofazimine
- E. Rifampin and ofloxacin

Answer: B The patient has lepromatous or borderline lepromatous leprosy with a high bacterial burden. His G6PD mutation is sufficiently severe (Chapter 161) that he is at high risk of significant hemolysis if he is treated with dapsone. Rifampin monotherapy is likely to select for rifampin-resistant variants, especially in someone with the high bacterial burden present in multibacillary leprosy. According to current guidelines, the only recommended drug to substitute for dapsone is clarithromycin. Reference: [http:// www.hrsa.gov/hansensdisease/diagnosis/recommendedtreatment.html](http://www.hrsa.gov/hansensdisease/diagnosis/recommendedtreatment.html)

2. A 27-year-old Brazilian woman was diagnosed with borderline tuberculoid leprosy on the basis of clinical and histopathologic criteria and was begun on multidrug therapy with dapsone and rifampin. Six months after initiation of therapy, she complains of worsening of her skin lesions, which are now more erythematous, and worsening neuritic pain with weakness of her left hand. She is afebrile, and a complete blood count and urinalysis are normal. What is the most appropriate therapeutic intervention?

- A. Add ofloxacin and clarithromycin for drug-resistant leprosy with progression.
- B. Discontinue rifampin and treat with thalidomide.
- C. Hold rifampin and add clofazimine and prednisone.
- D. Continue rifampin and dapsone and treat with prednisone until symptoms resolve.
- E. Biopsy the edge of one of the skin lesions and treat according to the results.

Answer: C The patient has typical symptoms and findings of a reversal reaction, which requires effective anti-inflammatory therapy to minimize progressive peripheral nerve damage. Reversal reactions are currently diagnosed clinically; a skin biopsy is not necessary. When there is evidence of nerve involvement during a reversal reaction, most experts recommend holding rifampin to minimize the ongoing release of pro-inflammatory components during bacterial death. The preferred treatment is clofazimine, owing to its anti-inflammatory activity; its additional antimycobacterial activity is thought to help minimize emergence of dapsone-resistant bacteria. When there is evidence of neural involvement, prompt addition of prednisone is indicated. Emergence of drug resistance during treatment of leprosy with a low bacterial burden, such as in borderline tuberculoid leprosy, occurs rarely and more often presents as a relapse rather than progression with evidence of increased inflammation. Thalidomide is used to treat erythema nodosum leprosum (ENL), not reversal reactions, and must be used with extreme caution and multiple methods of contraception in a woman of child-bearing age.

3. A 32-year-old man originally from Indonesia was found to have borderline tuberculoid leprosy during evaluation of a mononeuropathy. Results of a complete blood count, serum chemistry panel, and G6PD assay were all within normal limits. Four weeks after beginning treatment with dapsone and rifampin, he had gradual onset of malaise, fever, and diffuse rash. Physical examination is remarkable for a toxic appearance, fever (38.6° C), tachycardia, exfoliative dermatitis, diffuse lymphadenopathy, and hepatosplenomegaly. Lab studies are remarkable for leukocytosis, thrombocytopenia, and elevated transaminases. What intervention is most important for his recovery from the acute illness?

- A. Addition of thalidomide to his current regimen.
- B. Substitute clarithromycin for rifampin.
- C. Add clofazimine for antimycobacterial and anti-inflammatory activity.
- D. Add prednisone.
- E. Discontinue dapsone.

Answer: E The patient has dapsone hypersensitivity syndrome, which is an immunologically mediated reaction that is likely due to activation of CD8+ T cells. This syndrome has a case fatality rate as high as 10%, and when it occurs, dapsone must be discontinued immediately. A syndrome of systemic toxicity with the acute onset of rash in a patient receiving treatment for leprosy could also be erythema nodosum leprosum, but ENL occurs rarely if ever in patients with a low bacterial burden, as in tuberculoid or borderline tuberculoid leprosy.

4. A 72-year-old man from the Philippines was diagnosed with borderline lepromatous leprosy; treatment with rifampin, dapsone, and clofazimine was initiated. After 4 weeks, a reference laboratory reported that polymerase chain reaction (PCR) amplification of two separate skin biopsy samples revealed mutations in *Mycobacterium leprae* *polB* that are diagnostic of high-level rifampin resistance. How should his treatment be altered?

- A. Rifapentine should be substituted for rifampin.
- B. The dapsone dosage should be increased.
- C. Clarithromycin should be substituted for rifampin.
- D. Ofloxacin should be substituted for rifampin.
- E. Minocycline should be substituted for rifampin.

Answer: C Multidrug treatment of leprosy is essential for optimal relapse-free outcomes, especially in multibacillary leprosy, which includes borderline lepromatous leprosy. Although experience is limited, it is unlikely that treatment with dapsone and clofazimine is adequate for an optimal outcome. Mutations in *polB* that confer resistance to rifampin also confer resistance to other rifamycins, including rifabutin and rifapentine. Of the alternative drugs, clarithromycin is the only one currently recommended to substitute for rifampin.

5. In patients with lepromatous leprosy, in whom lesions contain very few T lymphocytes, nerve damage is thought to be due to which of the following mechanisms?

- A. Demyelination of peripheral nerve fibers by interaction of phenolic glycolipid with Schwann cells
- B. Autoantibody destruction of peripheral nerve axons
- C. TH1-mediated inflammatory tissue damage
- D. Cytolytic CD8+ T-cell expression of granzyme B
- E. Complement-mediated cytotoxicity

Answer: A In multibacillary (including lepromatous) leprosy, existing evidence is most consistent with nerve fiber damage by products of *M. leprae* rather than by host-mediated mechanisms. *M. leprae* phenolic glycolipid interacts with Schwann cell laminin 2 and activates the receptor tyrosine kinase ErbB2. Downstream signaling that requires activation of the Erk1/2 kinase(s) results in demyelination. In contrast, nerve damage in paucibacillary leprosy is believed to be mediated by host T-cell responses.

1. A 50-year-old man with acute Q fever presents after 7 days of fever, when he became spontaneously afebrile. You should:

- A. Prescribe 15 days of doxycycline.
- B. Evaluate clinically and/or echocardiographically if he has an underlying cardiovascular predisposing factor to chronic endocarditis.
- C. Perform hepatic echography to detect hepatomegaly.
- D. Explain to the patient that as he is spontaneously cured, he does not need to follow up.
- E. Investigate the possible environmental source of the disease.

Answer: B It is critical in such patients to determine the risk of endocarditis. Progression to chronic endocarditis may be accompanied by only low-grade or intermittent fever, but if it is not diagnosed it can cause severe valve dysfunction, heart failure, and embolic complications.

2. A 6-year-old boy is diagnosed with Rocky Mountain spotted fever and presents with high fever. You should prescribe:

- A. Treatment with doxycycline adjusted to weight
- B. Chloramphenicol intravenously
- C. Ciprofloxacin orally
- D. Erythromycin intravenously
- E. Ceftriaxone intravenously

Answer: A Doxycycline is recommended even in children for the treatment of potentially severe diseases. Oral treatment is effective.

3. A patient with body lice exposure and fever returns from Eastern Congo and you suspect louse-borne typhus. You should:

- A. Immediately prescribe two pills of 100 mg doxycycline.
- B. Prescribe intravenous chloramphenicol.
- C. Sample blood for serology and wait for the result to treat.
- D. Sample blood for polymerase chain reaction and wait for the result to treat.
- E. Sample a stain biopsy and wait for the result to treat.

Answer: A This situation is an emergency; the patient should be treated as soon as the diagnosis is suspected. The diagnosis of typhus should be clinical because the fatality rate is high and the treatment safe and effective.

4. A pregnant woman who travelled in Thailand received a diagnosis of scrub typhus. You should treat with which of the following:

- A. Doxycycline
- B. Ciprofloxacin
- C. Chloramphenicol
- D. Rifampicin
- E. Streptomycin

Answer: D Because doxycycline is a U.S. Food and Drug Administration Pregnancy Category C drug ("use not recommended unless essential for the patient's welfare."), rifampicin is the reference treatment for scrub typhus when doxycycline is contraindicated.

5. Which of these tick bite diseases may be commonly superinfected by yeast or opportunistic bacteria?

- A. Human monocytic ehrlichiosis
- B. Infection by *E. canis*
- C. Rocky Mountain spotted fever
- D. Human granulocytic anaplasmosis
- E. African tick bite fever

Answer: D Granulocytopenia favors superinfection by opportunistic pathogens.

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ZOONOSES

1. The deer tick (*Ixodes scapularis*) is a known vector for which of the following infections:

- A. Babesiosis
- B. Human monocytic ehrlichiosis (HME)
- C. Rocky Mountain spotted fever (RMSF)
- D. Leishmaniasis
- E. Chagas Disease

Answer: A HME and RMSF are transmitted by the bite of the Lone Star tick. Leishmaniasis is transmitted by the bite of a sandfly, and Chagas disease is spread by the kissing bug (Triatome).

2. Which of the following viral infections is associated with bats?

- A. Henipaviruses
- B. Dengue fever
- C. West Nile virus
- D. Avian H5N1 influenza
- E. Herpes simiae

Answer: A Henipaviruses, which include the Hendra virus and Nipah virus, are paramyxoviruses found in fruit bats in Australia and Asia, respectively.

3. A 32-year-old man with a history of Hodgkin's lymphoma in remission presents to the emergency department with a 3-day history of fever, cough, and left-sided pleuritic chest pain. He reports no recent travel or pets. One week prior to presentation, he had Thanksgiving dinner at his mother's house, where he remembered feeding table scraps to her dog. On admission, he is found to be febrile with a left lower lobe pneumonia and pleural effusion. Blood cultures drawn on admission are positive for a fastidious gram-negative rod that is most likely:

- A. *Streptococcus pneumoniae*
- B. *Haemophilus influenzae*
- C. *Pseudomonas aeruginosa*
- D. Methicillin-resistant *Staphylococcus aureus*
- E. *Pasteurella multocida*

Answer: E Transient contact with pets, including being licked by an animal, can result in transmission of pet-associated zoonoses such as *Pasteurella multocida*. Presumably in this case, the patient contacted the dog's saliva with his feeding hand and proceeded to eat without washing his hands. Patients with prior hematologic malignancies may be slow to fully recover immune function after completion of chemotherapy, and this may represent an added risk factor for infection.

4. A 12-year-old Kenyan boy presents with a necrotic ulcer on his right arm that has been present for approximately 2 weeks. The lesion started as a nonpainful papule, which gradually enlarged and eroded to leave a painless ulcer with a black necrotic-appearing base. He does not recall any trauma and works on the family farm herding cattle. On examination, the patient also has a low-grade fever with associated swollen right axillary lymph nodes. The most appropriate treatment would be:

- A. Penicillin
- B. Trimethoprim-sulfamethoxazole (TMP-SMX)
- C. Clindamycin
- D. Azithromycin
- E. Pentavalent antimony

Answer: A The patient has cutaneous anthrax, probably acquired from contact with cattle, and the treatment of choice is penicillin. TMP-SMX and clindamycin are reasonable treatment options for community-associated methicillin-resistant *Staphylococcus aureus* skin-soft tissue infections and impetigo. Azithromycin is used for treatment of cat-scratch disease or *Mycobacterium marinum* infection. Pentavalent antimony is generally used for treatment of cutaneous leishmaniasis (particularly New World cutaneous leishmaniasis).

5. A 50-year-old woman is admitted to the hospital for fevers and diffuse arthralgias and myalgias. She denies recent travel or pets. On examination, the patient has a faint diffuse rash over the extremities. Blood cultures drawn on admission are positive only at day 5 for a pleomorphic branching gram-variable rod that fails to grow on routine media. On further questioning, the patient admits to keeping a pet python and feeds it with rats. The most likely cause of her infection is:

- A. *Neisseria gonorrhoeae*
- B. *Streptococcus suis*
- C. *Bacillus anthracis*
- D. *Streptobacillus moniliformis*
- E. *Borrelia burgdorferi*

Answer: D The patient has rat-bite fever due to *Streptobacillus moniliformis*.

Ch / 329 ACTINOMYCOSIS

1. Which of the following statements is correct regarding treatment of actinomycosis?

- A. Treatment should be guided by in vitro antimicrobial susceptibility testing.
- B. Prolonged therapy with penicillin is limited by increasingly frequent acquisition of resistance to it.
- C. Cervicofacial and thoracic actinomycosis generally requires combination antimicrobial therapy.
- D. Penicillin G is the drug of choice and should be given in high doses for a prolonged period because the infection has a tendency to recur.
- E. Surgical intervention is almost never required if antibiotic therapy selection and duration are correctly prescribed.

Answer: D Penicillin G is the drug of choice for treatment of an infection caused by any of the actinomycoses. The infection has a tendency to recur, so high doses for prolonged periods are generally required. Little if any evidence exists for significant acquired resistance to penicillin G during prolonged therapy. The need for combination antimicrobial therapy to eradicate actinomycosis has not been established; however, it is often considered clinically appropriate, especially with lower abdominal infections. Effective antibiotic therapy does not replace the need for surgical intervention when needed, such as removal of necrotic tissue, fistula repair, and drainage. In vitro antimicrobial susceptibility testing of *Actinomycosis* is difficult and the results may not be predictive of in vivo effects.

2. Cervicofacial actinomycosis is:

- A. A rare manifestation of the infection.
- B. Usually caused by extension of primary intrathoracic involvement.
- C. Acutely accompanied by disproportionately severe symptoms of pain and trismus.
- D. Not prone to spread beyond the soft tissues of the neck, although its extension to those soft tissues can be extensive.
- E. A chronic disease.

Answer: C Cervicofacial infection is the most common manifestation of actinomycosis. It is generally odontogenic (not intrathoracic) in origin. Actinomycosis can be acute, subacute, or chronic. In its acute form, the symptoms of pain and trismus are disproportionate for the signs of inflammation that is apparent. Chronic actinomycosis can extend widely, including to the carotid arteries, tongue, sinuses, mastoid, orbit, thyroid, larynx, trachea, and contiguous muscle and bone.

3. Which of the following statements is correct regarding the epidemiology of actinomycosis?

- A. There is no person-to-person transmission.
- B. External reservoirs include soil and straw.
- C. Most diagnosed individuals are elderly.
- D. Males and females are comparably affected.
- E. It predominantly occurs in tropical climates.

Answer: A There is no evidence for person-to-person transmission or for any external environmental reservoirs (e.g., soil or straw) for actinomycosis. Ages of infected patients can range from childhood to old age, but peak incidence is in the middle decades of life. A male-to-female predominance (3 : 1 ratio) has been attributed to the increased prevalence of poor oral hygiene and oral trauma in males (because *Actinomyces* spp are endogenous flora of the oral cavity).

1. How can *Nocardia* be contracted by humans?

- A. Spread from person to person
- B. Spread from animals to humans (zoonotic infection)
- C. By inhaling dust
- D. By being bitten by mosquitoes
- E. By being bitten by ticks

Answer: C *Nocardia* usually gains entry through the lungs. Patients inhale dust contaminated with *Nocardia*, a common soil organism.

2. A 50-year-old male bicyclist fell on a dirt path, scraping his arm. Over the next 2 weeks he noted progressive swelling of his arm associated with swollen lymph nodes and streaks of erythema. He also developed a fever to 101° F. His peripheral WBC was 12,500 (90% PMN). How should you manage this patient (*best answer*)?

- A. Begin an antistaphylococcal antibiotic
- B. Swab the surface of his erythematous skin for culture
- C. Draw blood cultures
- D. Obtain a tissue biopsy for histopathologic examination and culture
- E. Obtain a urine antigen test for histoplasmosis

Answer: D Diagnosis of *Nocardia* is difficult and often delayed. Obtaining a biopsy sample for histopathologic examination and staining, as well as culture, is the primary method for making the appropriate diagnosis. Empirical antibiotics often fail to treat *Nocardia*. A surface swab culture is likely

to grow only normal skin flora because *Nocardia* is slow growing. *Histoplasma* rarely causes soft tissue infection, and therefore urine antigen is highly likely to be negative.

3. A 55-year-old renal transplant recipient, who has been receiving high-dose corticosteroids for transplant rejection, develops severe headaches that persist for 2 weeks. His headaches are sharp and localized to the left temporal region. They are not relieved by Tylenol or aspirin. He is admitted to the hospital after having a grand mal seizure that began with tonic-clonic movements of the right arm and leg. CT with contrast shows a multiloculated ring-enhancing abscess in the left temporal region. A CT-guided needle biopsy is performed. Gram stain of the sample demonstrates gram-positive beaded branching forms accompanied by many PMNs. What is the simplest and most rapid way to differentiate whether your patient has nocardiosis or actinomycosis?

- A. Modified acid-fast stain *Nocardia* is acid-fast positive
- B. Modified acid-fast stain *Actinomyces* spp are acid-fast positive
- C. Polymerase chain reaction of the sample
- D. Aerobic and anaerobic culture
- E. PET scan

Answer: A The *Nocardia* cell wall has a high lipid content that tightly binds carbol fuchsin (the red stain used for acid-fast staining) and is resistant to acid decolorization while *Actinomyces* spp is readily decolorized. PCR is most useful for speciation. It is more complicated to perform and is not readily available in most hospital-based diagnostic laboratories. *Nocardia* is slow growing and may take over a week to grow. PET scan can falsely diagnose *Nocardia* brain abscess as a brain tumor and is not a helpful diagnostic tool.

4. What would be the best treatment plan for a patient with a *Nocardia* brain abscess?

- A. Ceftriaxone and metronidazole combined with surgical drainage
- B. High-dose penicillin alone
- C. Trimethoprim-sulfamethoxazole combined with imipenem
- D. Clindamycin combined with surgical drainage
- E. Trimethoprim-sulfamethoxazole combined with imipenem and surgical drainage

Answer: E Trimethoprim-sulfamethoxazole continues to cover many strains of *Nocardia*; however, combination therapy is favored for brain abscess. Outcome is better when the abscess is also surgically drained. Penicillins have limited activity against *Nocardia*, as does ceftriaxone. Metronidazole has no activity and clindamycin fails to cross the blood-brain barrier and is not recommended for CNS infections.

5. How long should a patient with a *Nocardia* soft tissue infection be treated?

- A. 7 to 10 days
- B. 2 weeks
- C. 1 month
- D. 2 months
- E. 6 months

Answer: E *Nocardia* is an intracellular pathogen that grows slowly. Relapses have been observed if treatment is not extended for 6 months. In patients who are severely immunocompromised, 12 months of treatment may be required.

1. A 72-year-old man from Kentucky who has emphysema and coronary artery disease comes in with fever, night sweats, 20-lb weight loss, cough, and sputum production with occasional hemoptysis for the last 4 to 5 months. Chest x-ray shows bilateral upper lobe cavitory infiltrates and emphysematous changes. The *most* likely diagnosis is:

- A. Coccidioidomycosis.
- B. Sporotrichosis.
- C. Blastomycosis.
- D. Histoplasmosis.

Answer: D. Any of the above fungal infections can manifest by upper lobe cavitory lesions. However, the most likely diagnosis is histoplasmosis because he is from Kentucky, where *H. capsulatum* is highly endemic. Blastomycosis is also endemic in Kentucky but is less common than histoplasmosis. Pulmonary sporotrichosis could manifest with a similar picture, but is very uncommon. Coccidioidomycosis occurs in the desert southwest and is not possible unless he had traveled to that area.

2. Which test would be most useful for the diagnosis of chronic cavitory pulmonary histoplasmosis in the patient noted in question 1?

- A. Serum antigen assay for *H. capsulatum* cell wall polysaccharide
- B. CT scan of the chest
- C. Sputum culture for fungus
- D. PCR for *H. capsulatum* on serum
- E. Urine enzyme immunoassay

Answer: C. The definitive diagnostic test is growing *H. capsulatum* in culture, and in this form of histoplasmosis, sputum cultures usually yield the organism. PCR tests can be useful when performed on a tissue biopsy, but not on serum. The serum and urine antigen assays are not sensitive for the chronic cavitory form of histoplasmosis. CT scan is useful to define the extent of pulmonary disease, but it does not define the causative agent.

3. Which form of histoplasmosis does not respond to antifungal therapy?

- A. Chronic cavitory pulmonary
- B. Mediastinal fibrosis
- C. Disseminated infection in immunocompetent patients
- D. Acute respiratory distress syndrome (ARDS)
- E. Disseminated infections in patients with AIDS

Answer: B. Mediastinal fibrosis is characterized by an abnormal host response with the production of excessive fibrosis that can lead to obstruction of pulmonary arteries, the superior vena cava, and mainstem bronchi. The organism is rarely seen within the fibrous tissue, and it is thought that there is no longer active infection when the patient presents with obstructive symptoms. Disseminated histoplasmosis, including in patients with AIDS, and acute and chronic pulmonary histoplasmosis, including in patients with AIDS, respond to antifungal therapy.

4. A 65-year-old man is admitted with fevers and hypotension. He has a 3-month history of night sweats and weight loss, and he is found to have anemia (Hb 9.5 g/dL), thrombocytopenia (platelets 112,000/ μ L), and leukopenia (2600 WBC/ μ L). His serum sodium is 126 mEq/L and potassium is 5.2 mEq/L. What is the most likely fungal infection that could explain these findings?

- A. Coccidioidomycosis
- B. Sporotrichosis
- C. Histoplasmosis
- D. Cryptococcosis
- E. Candidiasis

Answer: C. The patient has adrenal insufficiency, and the fungus that most often causes this is *H. capsulatum*. The other fungal infections have been reported very rarely to cause adrenal insufficiency. This manifestation is not uncommon in patients with AIDS who develop disseminated histoplasmosis and in older adults who develop the chronic progressive form of disseminated histoplasmosis.

5. A 37-year-old woman is being treated with etanercept for rheumatoid arthritis. She developed disseminated histoplasmosis 3 weeks after an old barn on her farm had been demolished. On admission to hospital, she has hypoxemia, pancytopenia, and signs of disseminated intravascular coagulation. She should be treated with:

- A. Liposomal amphotericin B.
- B. Itraconazole.
- C. Amphotericin B deoxycholate.
- D. Fluconazole.

Answer: A. Liposomal amphotericin B has been shown to be superior to amphotericin B deoxycholate for the treatment of severe disseminated histoplasmosis in patients with AIDS. Mortality was decreased, patients became afebrile sooner, and toxicity was less with the liposomal formulation. Any immunosuppressed patient who has severe histoplasmosis should be treated with this agent. Itraconazole is appropriate therapy for mild-to-moderate histoplasmosis and for step-down therapy after the patient has responded to amphotericin B. Fluconazole is less active against *H. capsulatum* and is a second-line agent.

Ch / 333 COCCIDIOIDOMYCOSIS

1. A patient in Seattle, Washington is diagnosed with community-acquired pneumonia that developed 2 weeks after attending a business conference in Phoenix, Arizona. The likelihood that the etiology of the infection is *Coccidioides* is:

- A. 80%
- B. 30%
- C. 15%
- D. 5%
- E. Less than 1%

Answer: B Two prospective studies demonstrate this frequency within the endemic region. It is equally applicable to visitors with symptoms soon after endemic exposure.

2. A 56-year-old man, a long-time smoker who lives in the California central valley, is found to have a 2.5-cm right middle lobe nodule. He was diagnosed with valley fever 5 years ago. Evaluation should include:

- A. Repeated CT scans every 6 months to determine if the nodule is enlarging.
- B. Initiation of fluconazole 400 mg/day and re-evaluation for regression of the nodule.
- C. Obtain tissue for microscopic examination, either by bronchoscopy or percutaneous fine-needle aspiration.
- D. Perform edge resection by thoracotomy.
- E. Obtain a coccidioidal serology.

Answer: C There is insufficient information to assume the nodule is related to the prior coccidioidal diagnosis. It is too large to simply observe in a patient at risk for lung cancer. There is a high probability (perhaps 50%) that the nodule is not cancer, which would make the thoracotomy overly invasive without first establishing that the lesion is a cancer. Antifungal treatment would be unlikely

to affect the nodule size. Whether the coccidioidal serologic test was positive should not change the need for tissue to exclude cancer.

3. A patient develops coccidioidal meningitis, is started on fluconazole 400 mg/day and over the next 6 months completely resolves her symptoms. An MRI of the brain was never abnormal, and a follow-up lumbar puncture produces CSF with essentially normal laboratory values. Treatment is continued unchanged for 2 years. At that point, management should be:

- A. Stop treatment and follow-closely for possible relapse.
- B. Stop treatment only if reevaluation shows no evidence of pulmonary or extrapulmonary infection.
- C. Continue treatment at a reduced dose.
- D. Continue treatment at the current dosage indefinitely

Answer: D Relapses are frequent and potentially lethal. Even reducing the dose may lead to recurrence of infection.

4. A patient is found to have a thin-walled pulmonary cavity, 2 cm in diameter, abutting the visceral pleura in the left upper lobe. He has no symptoms associated with this. A coccidioidal complement fixation antibody test of serum returns a positive result at a 1 : 4 dilution. Management of this situation should be:

- A. No treatment, with periodic reassessment with chest x-ray.
- B. Start fluconazole 400 mg/day to see if the cavity responds to treatment by decreasing.
- C. Start amphotericin B intravenously.
- D. Resect the cavity by visually assisted transthoracic surgery (VATS) to avert the risk for cavity rupture and consequent bronchopleural fistula formation.

Answer: A Such cavities often follow an uncomplicated course. Treatment with antifungal agents does not affect the likelihood of their getting smaller. Although rupture occurs in some, most do not.

5. A woman in El Paso, Texas develops arthralgias in both ankles and erythema nodosum. She has no pulmonary symptoms. An enzyme immunosorbant assay for coccidioidal antibodies is positive for IgG antibodies. Which of the following is the *best* assessment of this current illness?

- A. Because the EIA IgG finding indicates past infection, the etiology still is not clear.
- B. This is likely the “desert rheumatism syndrome” of coccidioidomycosis.
- C. The skin lesions are likely to become progressive destructive lesions, and biopsy should be performed to determine how best to treat the patient.
- D. This presentation increases the likelihood that the patient eventually will develop serious complications.

Answer: B Because coccidioidal serology findings usually return to undetectable levels months following a coccidioidal infection, B is the correct answer. Patients with *E. nodosum* seldom develop future complications. A biopsy sample of the skin lesions would show an inflammatory process that is not specific to a particular etiology.

1. A 64-year-old previously healthy man from upper Michigan developed two skin lesions on his face and one on his thigh in late summer. He remembered having several days of feeling feverish with myalgias and a dry cough a few weeks before the first skin lesions appeared. He had been clearing brush around his home in early summer. On examination, he had three heaped-up, nontender lesions, two of which had punctate areas draining a small amount of purulent material on his face and left thigh. Chest radiograph revealed a left upper lobe infiltrate. Biopsy of one of the skin lesions revealed a pyogranulomatous tissue response and special stains showed thick-walled yeasts with a single broad-based budding daughter cell. The *most* likely etiology of this patient's skin lesions and pulmonary infiltrate is:

- A. Coccidioidomycosis.
- B. Histoplasmosis.
- C. Blastomycosis.
- D. Sporotrichosis.
- E. Disseminated cryptococcosis.

Answer: C Blastomycosis occurs throughout the Mississippi River Valley, in the north central states around the Great Lakes, and along the St. Lawrence Seaway. Blastomycosis begins as a pulmonary infection, but this may cause few symptoms and go undetected until a skin lesion develops. The skin lesions can be ulcers, papules, nodules, or plaques and often evolve to become verrucous with punctate draining areas in the center. Biopsy of a skin lesion shows an exuberant epidermal reaction known as *pseudoepitheliomatous hyperplasia*. Special stains should be performed to look for the distinctive large round, thick-walled yeasts that have a single broad-based budding daughter cell attached, allowing a tentative diagnosis of blastomycosis. Coccidioidomycosis occurs in the desert Southwest and not the upper Midwest. The skin lesions of histoplasmosis are generally smaller papules and usually appear in patients with systemic symptoms of disseminated infection. The skin lesions of sporotrichosis are rarely disseminated; they usually occur in the distribution of the lymphatic drainage from the initial inoculation site. Skin lesions are a prominent clue to disseminated cryptococcal infection in individuals with AIDS and other immunocompromised conditions.

2. The treatment of choice for mild-to-moderate disseminated blastomycosis is:

- A. Fluconazole.
- B. Itraconazole.
- C. Micafungin.
- D. Voriconazole.
- E. Amphotericin B.

Answer: B Itraconazole is the drug of choice for the treatment of most of the endemic mycoses, and the most experience has accrued with this agent. If itraconazole is not tolerated, the second choice for blastomycosis should be voriconazole, which is increasingly used for the treatment. Fluconazole is not as active, and high doses must be given if the patient is treated with this agent. Micafungin and the other echinocandins are not active against the endemic mycoses. Amphotericin B is reserved as initial therapy for severe blastomycosis.

3. A patient presents with a single skin lesion on her left cheek that yields *B. dermatitidis*. Chest radiograph reveals no pulmonary infiltrate. The most likely mechanism of infection with this organism was:

- A. Inoculation when a twig scratched her cheek.
- B. Ingestion of mold-contaminated unwashed vegetables.
- C. Inoculation of conidia when she rubbed her face while gardening.
- D. Inhalation of conidia of the mold phase from the soil.

Answer: D Blastomycosis results when conidia are inhaled into the lungs from the soil or decaying vegetation where the organism is growing. The organism is ingested by macrophages and converts into the yeast phase. Spread occurs by the hematogenous route, and the skin is the most common site of dissemination. The pulmonary infection may be healed by the time the patient presents with skin lesions. Even one skin lesion is a manifestation of hematogenous spread unless a clear-cut inoculation event has been documented. The organism is never acquired by ingestion.

4. Which is the most definitive diagnostic test for blastomycosis?

- A. Culture of a skin lesion
- B. PCR for *B. dermatitidis* in serum
- C. Antigen detection in a sputum sample
- D. Complement fixation antibody tests

Answer: A Culture is always definitive for the endemic mycoses, which are environmental organisms and never colonizers of humans. PCR can be useful if performed on tissue samples, but is not useful for serum. A *B. dermatitidis* antigen assay is available for urine and serum, but cannot be performed on sputum samples. Antibody assays are not specific or sensitive for infection with *B. dermatitidis*.

5. A patient presents with acute respiratory distress syndrome (ARDS) several weeks after returning from a hunting trip in northern Wisconsin. Bronchoalveolar lavage reveals large yeasts with single broad-based buds seen on calcofluor white stain. The most appropriate treatment would be:

- A. Itraconazole, 200 mg PO twice daily
- B. Lipid formulation amphotericin B, 5 mg/kg/day IV
- C. Posaconazole, 400 mg PO twice daily
- D. Caspofungin, 50 mg/day IV
- E. Voriconazole, 200 mg PO twice daily

Answer: B Persons seriously ill with blastomycosis, which is the most likely diagnosis given the organism seen on the calcofluor stain of the BAL, require treatment with amphotericin B. Most physicians now use a lipid formulation to decrease the risks for nephrotoxicity. Oral azole agents should not be relied on for therapy in a seriously ill patient. Caspofungin and the other echinocandins are not active against *B. dermatitidis* or other endemic mycoses.

Ch / 335 PARACOCCIDIOIDOMYCOSIS

1. To entertain a diagnosis of paracoccidioidomycosis, one should obtain a history of residence in:

- A. The Mideast.
- B. South America.
- C. Southeast Asia.
- D. North America.
- E. Africa.

Answer: B The geographic distribution of *Paracoccidioides brasiliensis* is in several countries in South America. It does not occur in any of the other areas listed.

2. The usual hosts in whom chronic paracoccidioidomycosis is seen are:

- A. Infants.
- B. Teenage girls.
- C. Middle-aged men.
- D. Older women.
- E. Immunocompromised individuals.

Answer: C Chronic paracoccidioidomycosis is seen almost entirely in middle-aged to older men. The male-to-female ratio is usually quoted as 13 : 1, but has been reported to be as high as 70 : 1 in some countries of South America. The infection begins earlier in life but is slowly progressive, and symptoms appear in middle age. The propensity for infection to occur in men has been explained both by greater exposure to the organism and by the protective effect of estrogens on infection in women.

3. The treatment of choice for paracoccidioidomycosis is:

- A. Posaconazole.
- B. Amphotericin B.
- C. Caspofungin.
- D. Itraconazole.

Answer: D Itraconazole is the preferred treatment of paracoccidioidomycosis. There is little experience with posaconazole, but it has been shown to be effective. Caspofungin and other ecinocandins have no activity against *P. brasiliensis* or other endemic mycoses. Amphotericin B is reserved for treatment of severe infection, such as occurs in immunocompromised patients.

4. A major complication of chronic paracoccidioidomycosis in spite of antifungal therapy is:

- A. Pulmonary fibrosis.
- B. Granulomatous mediastinitis.
- C. Constrictive pericarditis.
- D. Pneumothorax.
- E. Retroperitoneal fibrosis.

Answer: A Pulmonary fibrosis can progress in patients who have the chronic form of paracoccidioidomycosis, in spite of treatment. Progression is more likely in those who have more extensive pulmonary infection. Granulomatous mediastinitis occurs with histoplasmosis, but is uncommon with paracoccidioidomycosis. Constrictive pericarditis is not a complication of paracoccidioidomycosis, and pneumothorax is not commonly seen.

5. In patients who have HIV infection, paracoccidioidomycosis can be a life-threatening acute infection and should be treated with:

- A. Itraconazole.
- B. Voriconazole.
- C. Amphotericin B.
- D. Trimethoprim-sulfamethoxazole.
- E. Combination antifungals.

Answer: C HIV-infected patients develop acute disseminated paracoccidioidomycosis and should be treated with amphotericin B initially. Step-down therapy to itraconazole can be given after they have improved. Trimethoprim-sulfamethoxazole is effective for paracoccidioidomycosis, but should not be used for severe infection as initial therapy. Voriconazole also is effective for paracoccidioidomycosis, but should not be used for severe infection as initial therapy.

1. A patient with cryptococcal meningitis had improvement of headache and nausea following the initial diagnostic lumbar puncture. Amphotericin B and flucytosine were begun immediately after the tap, but 2 days later, he has recurrence of these symptoms and also has some blurring of vision. What is the likely reason for the return of his symptoms?

- A. Reaction to amphotericin B
- B. Secondary bacterial infection related to the lumbar puncture
- C. Increased intracranial pressure
- D. Resistance of the organism to amphotericin B
- E. Resistance of the organism to flucytosine

Answer: C This is a typical picture in that the lumbar puncture takes off cerebrospinal fluid and relieves some of the pressure briefly. Increased intracranial pressure is most likely due to blockage of the arachnoid villi and/or increased brain edema and is thought to be secondary to the large capsule surrounding the yeast. Resistance to amphotericin B and flucytosine is very uncommon. The symptoms, especially blurring of vision, are unlikely due to amphotericin B toxicity. Secondary bacterial infection after a spinal tap is also rare.

2. What is the treatment for the condition noted in question 1?

- A. Perform repeated lumbar punctures to bring down the increased pressure
- B. Change therapy to fluconazole
- C. Continue amphotericin B but stop flucytosine
- D. Add ceftriaxone 2 g every 12 hours
- E. Symptomatic treatment only

Answer: A Treatment of increased intracranial pressure, which is seen commonly with cryptococcal meningitis, is to perform repeated spinal taps until the pressure remains low. There is no reason to change antifungal therapy or add an antibiotic.

3. Which of the following is the preferred treatment for an AIDS patient with cryptococcal meningitis?

- A. Fluconazole and flucytosine
- B. Voriconazole and amphotericin B
- C. Posaconazole and caspofungin
- D. Amphotericin B and flucytosine
- E. Fluconazole

Answer: D Several randomized blind and open-label treatment trials have shown the benefit of combined therapy with amphotericin B and flucytosine for cryptococcal meningitis. Echinocandins have no role in treating this infection. The other suggested regimens are inferior to amphotericin B and flucytosine.

4. What is the major host defense against *Cryptococcus* species?

- A. Immunoglobulin A antibody
- B. Natural killer cells
- C. T lymphocytes
- D. Complement
- E. Neutrophils

Answer: C Patients who have deficient T-cell immunity, such as AIDS patients with low CD4 cell counts, transplant recipients, and patients on corticosteroids, are at high risk for developing infection with *Cryptococcus*.

5. The diagnosis of cryptococcal meningitis can be made in a few hours by performing which of the following?

- A. Culture of cerebrospinal fluid
- B. Magnetic resonance imaging
- C. Lateral flow dipstick test for cryptococcal antigen
- D. Cryptococcal immunoglobulin M antibody assay
- E. Gram stain of cerebrospinal fluid

Answer: C Culture is definitive but takes several days. Antibody assays for *Cryptococcus neoformans* are not helpful for diagnosis. Magnetic resonance imaging may show brain abscesses and meningeal enhancement, but these are not specific for cryptococcosis. The dipstick method for detecting antigen in cerebrospinal fluid is a rapid, sensitive, and specific test to make the diagnosis of cryptococcal meningitis. An India ink preparation (but not Gram stain) allows visualization of the budding yeast cells surrounded by the large capsule, but this test is not currently done by many laboratories.

Ch / 337 SPOROTRICHOSIS

1. A 26-year-old man from Michigan had a motorcycle collision; he was thrown off and scraped his left shoulder in the dirt. Two weeks later, he developed a nodular lesion at the site of the injury. This ulcerated, and then several other nodular lesions that became ulcerated appeared proximal to the initial lesion over the next 3 weeks. He had no systemic symptoms or signs of infection. What is the most likely organism causing this infection?

- A. *Leishmania brasiliensis*
- B. *Mycobacterium marinum*
- C. *Nocardia asteroides*
- D. *Sporothrix schenckii*

Answer: D This is a typical picture of lymphocutaneous sporotrichosis due to inoculation of *S. schenckii* from soil into the skin and subcutaneous tissues. Days to weeks after inoculation, a papule develops at the site of inoculation. The primary lesion can become nodular, but most often, it ulcerates. The drainage is not grossly purulent and has no odor, and the lesion is not terribly painful. *M. marinum* is usually associated with water exposure. *L. brasiliensis* is not found in North America. *Nocardia* species usually cause infection in immunocompromised hosts.

2. Which of the following is the most appropriate method for establishing the diagnosis of sporotrichosis?

- A. Culture of the fungus from a skin lesion
- B. Polymerase chain reaction (PCR) on a serum sample
- C. Antibody testing
- D. Antigen assay in urine
- E. Histopathology

Answer: A There is no sensitive or specific antibody or antigen assay for *S. schenckii*. PCR can be performed at reference laboratories on tissue, but not on serum. Histopathology of biopsy material shows a mixed granulomatous and pyogenic process, but the organisms are often present in small numbers and frequently not visualized. Culture of a lesion is the definitive diagnostic procedure for sporotrichosis.

3. Which of the following is the treatment of choice for lymphocutaneous sporotrichosis?

- A. Posaconazole
- B. Itraconazole
- C. Voriconazole
- D. Fluconazole
- E. Saturated solution of potassium iodide (SSKI)

Answer: B Itraconazole is the treatment of choice for lymphocutaneous sporotrichosis. Fluconazole has some activity, but large doses are needed to be effective. Voriconazole does not have activity against *S. schenckii*, and there are minimal data with posaconazole. SSKI has been used to treat sporotrichosis for almost a century, but it has many side effects, and its only advantage is that it is not expensive.

4. Which animal is most often implicated in zoonotic transmission of *S. schenckii* to humans?

- A. Armadillos
- B. Dogs
- C. Pigs
- D. Cats
- E. Birds

Answer: D Cats have been associated with an ongoing outbreak since 1998 of sporotrichosis in Rio de Janeiro; this outbreak involves mostly children and women who care for the cats, which are infected and generally have a high burden of organisms. Dogs have only occasionally been involved in transmission of sporotrichosis to humans. Armadillos can transmit *S. schenckii* to humans by inoculating the organisms from dirt on their claws. Pigs and birds have not transmitted *S. schenckii*.

5. Saturated solution of potassium iodide (SSKI) is effective in treating which manifestation of sporotrichosis?

- A. Osteoarticular
- B. Pulmonary
- C. Lymphocutaneous
- D. Disseminated
- E. Breast

Answer: C SSKI has been used for a century to treat sporotrichosis but is only effective against the cutaneous and lymphocutaneous forms. Pulmonary, osteoarticular, and disseminated infection, including unusual sites like breast, must be treated with either itraconazole or amphotericin B.

Ch / 338 CANDIDIASIS

1. *Candida glabrata* infections are more difficult to treat for which of the following reasons?

- A. *C. glabrata* is more virulent.
- B. *C. glabrata* cannot be phagocytized by neutrophils.
- C. *C. glabrata* is resistant to azole antifungals.
- D. *C. glabrata* readily forms hyphae and invades tissues.

Answer: C *C. glabrata* infections are difficult to treat because of both inherent and acquired resistance to fluconazole and other azoles. It is not more virulent and may actually be less so. It does not form hyphae in contrast to the other species of *Candida*. Phagocytosis of *C. glabrata* occurs just as it does with other *Candida* species.

2. An AIDS patient comes in because he has retrosternal pain when he swallows. He does not have thrush, and there is no cervical lymphadenopathy. What is the most likely diagnosis?

- A. Gastroesophageal reflux disease
- B. Pericarditis
- C. Pulmonary embolus
- D. Esophageal candidiasis
- E. Angina

Answer: D Odynophagia is the classic symptom shown by AIDS patients who have *Candida* esophagitis. The other diseases generally do not cause pain when swallowing food. Esophagitis can occur without thrush, although frequently both are present concomitantly. Response to treatment with fluconazole can be used as a diagnostic test for *Candida* esophagitis; endoscopy can be done, also, but is usually reserved for patients who do not respond to fluconazole therapy.

3. Which is *not* a risk factor for candidemia?

- A. High APACHE II score
- B. Central venous catheter
- C. Deficient T-cell immunity
- D. Prior surgical procedure
- E. Neutropenia

Answer: C The risk factors for candidemia include everything noted above except deficient T-cell immunity. T cells are important in protection against mucosal infection with *Candida* species but do not play a role in prevention of invasive candidiasis and candidemia.

4. A 70-year-old man who is in the intensive care unit after having abdominal surgery for a perforated bowel becomes hypotensive and febrile. He has a central catheter in place, is receiving parenteral nutrition and broad-spectrum antibiotics, and has kidney failure requiring renal replacement therapy. What is the most appropriate approach to treatment after you obtain blood cultures?

- A. Treat with fluconazole when the laboratory tells you that yeasts are growing in the cultures.
- B. Treat with an echinocandin after the laboratory identifies the yeast in the blood cultures as *C. glabrata*.
- C. Treat with amphotericin B immediately after obtaining the blood cultures.
- D. Treat with fluconazole after the laboratory identifies the yeast in the blood culture as *C. glabrata*.
- E. Treat with an echinocandin immediately after obtaining the blood cultures.

Answer: E In a patient at great risk for candidemia, as is this patient (who is on renal replacement therapy, has a central venous catheter plus another central line for dialysis, is receiving broad-spectrum antibiotics and parenteral nutrition, has a perforated bowel, and has undergone recent abdominal surgery), empirical treatment with an antifungal agent should be started as soon as the blood cultures and any other pertinent cultures have been obtained. Amphotericin B is rarely used in this setting, and echinocandins or fluconazole are generally used. In a patient who is not stable and is hypotensive, an echinocandin is preferred. Waiting for the cultures to grow, which will take 1 to 3 days, and for identification of species, which may add another 2 to 3 days, increases the mortality rate enormously in candidemic patients.

5. Which finding is helpful in directing the clinician to a diagnosis of invasive candidiasis?

- A. Nonpainful papular skin lesions on an erythematous base on the chest and left arm
- B. Painful erythematous nodules developing on the shins
- C. Bilateral spreading erythema over the lower legs and feet
- D. Molluscum-type lesions on the forehead accompanied by fever
- E. Pruritic blisters appearing in crops over the trunk

Answer: A Candidemia and invasive candidiasis can present with the sudden appearance of nonpainful, nonpruritic papules that evolve to become pustules on an erythematous base. These can occur anywhere on the body. All of the other lesions do not occur with candidemia.

Ch / 339 ASPERGILLOSIS

1. Which of the following statements is correct regarding the treatment of invasive aspergillosis?

- A. Reversal of immunosuppression is critical for successful therapy.
- B. Combination antifungal therapy, including a triazole, is the treatment of choice because monotherapy is usually not effective.
- C. There are no biomarkers that can be clinically used for following response to treatment.
- D. Surgical treatment is rarely needed when long-term, uninterrupted antifungal treatment can be administered.
- E. Systemic antifungal therapy is sufficient to treat ocular involvement.

Answer: A Invasive aspergillosis characteristically occurs in immunocompromised hosts. In these individuals, reversal of immunosuppression (e.g., recovery from neutropenia, discontinuation of corticosteroids) is a critical factor in successful management. The antifungal treatment of choice for invasive aspergillosis, according to Infectious Diseases Society of America clinical practice guidelines, is monotherapy with voriconazole; the alternate drug is liposomal amphotericin B. Second-line and salvage treatments likewise involve monotherapy. Surgical treatment is an important adjunctive component of primary therapy for several forms of invasive aspergillosis (e.g., endocarditis, osteomyelitis, epidural abscess, soft tissue infection, and others). Intravitreal antifungal therapy for endophthalmitis and topical irrigation with an antifungal agent for keratitis can provide high concentrations of these agents to ocular compartments that may not be reached by systemic therapy. Galactomannan and (1→3)-β-d-glucan in serum or bronchoalveolar lavage are useful biomarkers.

2. Which of the following statements is correct regarding treatment of different forms of chronic aspergillosis?

- A. Long-term voriconazole has a high success rate in curing aspergilloma.
- B. Bronchial artery embolization is an effective alternative for curing aspergilloma.
- C. Response to antifungal therapy for chronic necrotizing pulmonary aspergillosis is conveniently monitored by serial computed tomography (CT).
- D. Surgical resection is recommended for definitive therapy of solitary aspergilloma and chronic cavitary pulmonary aspergillosis.
- E. Surgical resection plays an important role in treating disease complicated by hemoptysis.

Answer: E Surgical resection may have an important role in treating patients with recurrent and severe hemoptysis. However, in general, surgical resection in patients with solitary aspergilloma or chronic necrotizing pulmonary aspergillosis is limited by complications of bronchopleural fistula development, *Aspergillus* infection of the pleural space, and potential further worsening of already compromised pulmonary function. Medical therapy has limited benefit in the treatment of aspergilloma. Although some benefit may be derived from extended use of an antifungal triazole, lifelong commitment to it should be balanced against the natural history of spontaneous resolution in about 10% of patients. Bronchial artery embolization (or transthoracic direct intracavitary instillation of antifungal agents) for aspergilloma has only transient benefits but substantial risk. CT or radiologic assessment of response to antifungal therapy in chronic necrotizing pulmonary aspergillosis is difficult because of the underlying chronic lung disease.

3. Allergic bronchopulmonary aspergillosis (ABPA) occurs most frequently in patients with which of the following?

- A. Intravenous drug abuse
- B. Immunocompromised status
- C. Asthma
- D. α 1-Antitrypsin deficiency
- E. Occupational exposure (e.g., malt workers)

Answer: C ABPA characteristically develops in patients with a history of chronic asthma or cystic fibrosis (not α 1-antitrypsin deficiency). ABPA is characterized by episodic airway obstruction, fever, eosinophilia, mucous plugs containing hyphae, transient infiltrates and parallel “tramline” or ring markings on chest radiographs, bronchiectasis, and upper lobe contraction. Extrinsic allergic alveolitis, an unusual allergic form of *Aspergillus* lung disease, is associated with *Aspergillus clavatus* in malt workers. In contrast, invasive aspergillosis is seen in immunocompromised patients and those with intravenous drug abuse.

Ch / 340 MUCORMYCOSIS

1. What is the best way to diagnose mucormycosis?

- A. Serum galactomannan
- B. Serum β -d-glucan
- C. Anti-Mucorales antibodies
- D. Polymerase chain reaction (PCR)
- E. Tissue for biopsy and culture

Answer: E Unfortunately, there are no biomarkers to diagnose mucormycosis, and this is a major unmet need for the management of the disease. Specifically, galactomannan and β -d-glucan do not detect Mucorales. PCR, although promising, remains investigational. There are no data about the value of anti- Mucorales antibodies for diagnosis. Tissue for histopathologic analysis and culture remains the only method for documenting invasive disease. (See Skiada A, Lanternier F, Groll AH, et al. Diagnosis and treatment of mucormycosis in patients with haematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia [ECIL 3]. *Haematologica*. 2013;98[4]:492-506; and Tacke D, Koehler P, Markiefka B, Cornely OA. Our 2014 approach to mucormycosis. *Mycoses*. 2014;57[9]:519-524.)

2. All the conditions below are common risk factors for mucormycosis *except* which one of the following?

- A. Iron overload
- B. Poorly controlled diabetes
- C. Crowding conditions
- D. Severe trauma of soft tissues
- E. Chronic severe immune suppression

Answer: C Classic risk factors for the disease include iron overload that results in increased availability of host iron to support invasive fungal growth, significant and chronic immunosuppression such as severe cytopenia, systemic corticosteroids, crushing soft tissue injury (e.g., following severe trauma), and poorly controlled diabetes, especially in the setting of acidosis. Mucorales are extremely rare causes of catheter related infections not known to be associated with crowding conditions in the absence of trauma. (See Epidemiology.)

3. What is the most common Mucorales species causing mucormycosis?

- A. *Mucor* spp
- B. *Cunninghamella bertholletiae*
- C. *Rhizomucor* spp
- D. *Rhizopus* spp
- E. *Apophysomyces* spp

Answer: D Although there is notable geographic and host-related variability of infecting Mucorales, on a global scale *Rhizopus* species are the most common cause of mucormycosis, accounting for nearly 50% of such cases. (See Epidemiology.)

4. Which of the following azoles has the most potent activity against Mucorales?

- A. Fluconazole
- B. Posaconazole
- C. Voriconazole
- D. Itraconazole
- E. Ketoconazole

Answer: B Mucorales are innately resistant to most antifungal drugs. Specifically, the only agents that have activity are amphotericin B and the triazole posaconazole. (See Skiada A, Lanternier F, Groll AH, et al. Diagnosis and treatment of mucormycosis in patients with haematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia [ECIL 3]. *Haematologica*. 2013;98[4]:492-506; Tacke D, Koehler P, Markiefka B, Cornely OA. Our 2014 approach to mucormycosis. *Mycoses*. 2014;57[9]:519-524; and Kontoyiannis DP, Lewis RE. How I treat mucormycosis. *Blood*. 2011;118[5]:1216-1224. Also see section Treatment.)

Ch / 341 PNEUMOCYSTIS PNEUMONIA

1. A 47 year old previously healthy male comes into the emergency room complaining of a 2 week history of shortness of breath, non-productive cough, and fevers to 103° C. On physical exam he is tachypneic, with no rales or rhonchi, and has thrush on his buccal mucosa. His chest X-ray and pulse oximetry are normal. Which of the following is true?

- A. The normal chest X-ray and pulse oximetry rule out *Pneumocystis* pneumonia.
- B. A chest CT can help in the diagnosis of *Pneumocystis* pneumonia since it is almost invariably abnormal, even in the setting of a normal chest X-ray.
- C. A positive PCR test for *Pneumocystis* definitively confirms the diagnosis of *Pneumocystis* pneumonia as the specificity of the PCR test for PCP approaches 100%.
- D. Culture of induced, but not expectorated, sputum on Sabouraud agar will confirm the diagnosis of *Pneumocystis* pneumonia in 2 to 3 days.
- E. Bronchoscopy with bronchoalveolar lavage is helpful if positive for *Pneumocystis* but has a low sensitivity (~40-50%); open lung biopsy is required to confirm the diagnosis of PCP in about 50% of patients.

Answer: B This patient likely has undiagnosed HIV infection and *Pneumocystis* pneumonia based on the symptoms and presence of thrush. Patients presenting with *Pneumocystis* pneumonia can have a normal chest x-ray (CXR) and normal pulse oximetry or arterial oxygenation at rest. Even in patients with a normal CXR, a CT scan of the chest will invariably show infiltrates, as illustrated in Figure 341-2. PCR-based assays have a high sensitivity but the specificity does not approach 100% as it can also be positive in individuals who are colonized or subclinically infected with *Pneumocystis*, but do not have *Pneumocystis* pneumonia and do not require specific anti- *Pneumocystis* therapy. *Pneumocystis* cannot be cultured, so definitive diagnosis depends on direct detection of the organism in a clinical sample, usually an induced sputum or bronchoalveolar lavage sample. Bronchoscopy with

bronchoalveolar lavage has a >90% sensitivity for *Pneumocystis* pneumonia and is usually the definitive diagnostic procedure for *Pneumocystis* pneumonia. Prior to the AIDS epidemic and the demonstration of the utility of bronchoscopy, open lung biopsy was often required to make the diagnosis, but currently it is rarely necessary; negative results by bronchoscopy with BAL is sufficient to rule out *Pneumocystis* pneumonia in most circumstances.

2. A 25 year old female with a history of prior intravenous drug use comes in with a 1 week history of fever and a non-productive cough. CXR shows diffuse bilateral infiltrates. Resting PaO₂ at presentation is 96 mm Hg with an A-a gradient of 15 mm Hg. A rapid HIV test is positive. An induced sputum stain for *Pneumocystis* is positive, and the patient is started on trimethoprim-sulfamethoxazole, 2 double strength tablets 3 times a day. She is sent home to be followed in clinic. Three days later she returns complaining of increasing shortness of breath with walking. Resting PaO₂ has decreased to 86 mm Hg, with an A-a gradient of 30 mm Hg. What is the most appropriate management course for this patient?
- A. Discontinue the trimethoprim-sulfamethoxazole and begin pentamidine.
 - B. Discontinue the trimethoprim-sulfamethoxazole and begin clindamycin-primaquine.
 - C. Bronchoscope the patient to rule out other infections, and evaluate the patient for pulmonary emboli.
 - D. Begin prednisone 40 mg/day in addition to the trimethoprim-sulfamethoxazole.
 - E. Continue the trimethoprim-sulfamethoxazole; no change in therapy is needed.

Answer: E Deterioration in oxygenation at day 3 to 4 after start of therapy is common and expected in patients with PCP and does not signify clinical failure. Thus there is no reason to change therapy to an alternative regimen, or to search for alternative diagnoses at this point. While prednisone has been shown to decrease the frequency of deterioration in oxygenation in patients with PCP, a large randomized trial found that clinical benefit in terms of respiratory failure and survival outcome was limited to patients with moderate to severe disease, defined as a PaO₂ < 70 mm Hg or an A-a gradient >35 mm Hg. Moreover, addition of prednisone after 3 days of specific anti- *Pneumocystis* therapy has not been shown to be beneficial.

3. A 38 year old male with a recent history of thrush is admitted with a fever and non-productive cough. He is diagnosed with HIV infection and *Pneumocystis* pneumonia, and is started on trimethoprim-sulfamethoxazole. He would like to start anti-HIV medications soon. How should his anti-retroviral therapy be managed?
- A. Initiate HAART 2 months after discontinuation of anti-*Pneumocystis* therapy.
 - B. Initiate HAART immediately if HIV plasma viral load is >100,000 copies/ml, and 2 months after discontinuation of anti-*Pneumocystis* therapy if HIV plasma viral load is ≤100,000 copies/ml.
 - C. Timing of HAART should be based on the CD4 count. If the CD4 count is ≤350 cells/mm³, HAART should be initiated within 1 month of completion of therapy. If the CD4 count is >350 cells/mm³, therapy can be deferred until the cell count drops below that level.
 - D. Initiate HAART within 2 weeks of starting anti-*Pneumocystis* therapy if possible.
 - E. Don't initiate HAART until the CXR has normalized to minimize the risk of developing immune reconstitution inflammatory syndrome (IRIS).

Answer: D A randomized trial in patients with an opportunistic infection, 63% of whom had *Pneumocystis* pneumonia, found that initiation of HAART early (~12 days) vs. late (~45 days) after the start of therapy for the opportunistic infection was associated with a lower risk of AIDS progression or death. Patients with *Pneumocystis* pneumonia should be started on HAART regardless of the CD4 count or viral load, since they have already shown that their immune systems are severely compromised; without HAART or anti- *Pneumocystis* prophylaxis they are at high risk for recurrence of *Pneumocystis* pneumonia. Of note, most patients diagnosed with *Pneumocystis* pneumonia will have a CD4 count under 200 cells/mm³. While cases of IRIS in the setting of *Pneumocystis* pneumonia have been reported, the incidence appears to be relatively low and rarely appears to be life-threatening; in the randomized trial noted above, the incidence of IRIS in patients with *Pneumocystis* pneumonia was 7.3%.

4. A patient who received a renal transplant 6 months ago and is receiving mycophenolate mofetil, cyclosporine, and prednisone for chronic immunosuppression is diagnosed with *Pneumocystis* pneumonia. This is the fourth renal transplant patient diagnosed with *Pneumocystis* pneumonia during the past year. Renal transplant patients at this center do not routinely receive anti-*Pneumocystis* prophylaxis because no cases of *Pneumocystis* pneumonia were seen in the prior ten years. What is the best management strategy for stopping this outbreak of *Pneumocystis* pneumonia?
- A. Place the patient on respiratory isolation to prevent spread of the organism to other transplant patients.
 - B. Clean the walls, floors, and ceilings of the patient rooms in the clinic and inpatient service with bleach to eliminate the source of *Pneumocystis*.
 - C. Have the patients at risk for infection wash daily with a povidone-iodine antiseptic solution to minimize colonization with *Pneumocystis*.
 - D. Begin prophylaxis with trimethoprim-sulfamethoxazole in all transplant patients for at least 6 months, and longer for high risk patients (e.g. those requiring additional immunosuppression for graft rejection).
 - E. Begin prophylaxis with clindamycin-pyrimethamine in all transplant patients for at least 4 months, and longer for high risk patients (e.g. those requiring additional immunosuppression for graft rejection).

Answer: D Outbreaks of *Pneumocystis* pneumonia have been reported from multiple renal transplant centers over the past 10 years. As demonstrated in molecular typing studies, these outbreaks are caused by a single or a limited number of strains of *Pneumocystis* at each center. This strongly implies recent transmission of the infection, and potential acquisition as a nosocomial infection. Current data suggest that *Pneumocystis* is acquired from other humans via transmission by the respiratory route. There is no evidence for an environmental reservoir, thus cleaning a room will not eliminate the sources of infection. Although colonization or subclinical infection of the respiratory tract with *Pneumocystis* has been documented by sensitive PCR-based methods, there is no evidence that the skin is colonized, and thus washing with povidone-iodine antiseptic solution will not eliminate potential reservoirs for this specific organism. While it is logical to utilize respiratory isolation to prevent the spread of *Pneumocystis*, there are no data to demonstrate that this is an effective strategy to halt an outbreak. Infection may be spread during the incubation period, which in animal models, can be 8-12 weeks before the development of severe pneumonia. Clindamycin-pyrimethamine has not been demonstrated to have activity in either treatment or prophylaxis of *Pneumocystis* pneumonia. Trimethoprim-sulfamethoxazole is a highly effective prophylactic regimen and institution of prophylaxis with trimethoprim-sulfamethoxazole has been successful in halting the outbreaks of *Pneumocystis* pneumonia reported to date.

5. A 35 year-old female comes in with a headache and weakness in her right arm. An MRI scan shows multiple ring-enhancing lesions. Her anti-toxoplasma IgG antibody test is positive, but her IgM is negative. Cerebrospinal fluid is positive for *Toxoplasma* by PCR. Her HIV test is positive, and her baseline labs include a CD4 count of 27 cells/mm³ and an HIV viral load of 42,500 copies/ml. The patient noted that she had received trimethoprim-sulfamethoxazole many years ago for a urinary tract infection and said she thought she developed a rash around her elbows but did complete her therapy. She is started on pyrimethamine-sulfadiazine-leucovorin for treatment of CNS toxoplasmosis. How should anti-*Pneumocystis* prophylaxis be managed in this patient?
- A. No specific anti-*Pneumocystis* prophylaxis is required.
 - B. Begin dapsone 100 mg/day since she may have an allergy to trimethoprim-sulfamethoxazole.
 - C. Begin atovaquone 1,500 mg per day since she may have an allergy to trimethoprim-sulfamethoxazole and patients with sulfa allergies are frequently allergic to dapsone.
 - D. Begin azithromycin, 1,200 mg per week, to provide prophylaxis for both *Pneumocystis* and *Mycobacterium avium* complex.
 - E. Begin trimethoprim-sulfamethoxazole, one double-strength daily; change to dapsone if the patient develops a rash.

Answer: A This severely immunocompromised patient with HIV infection and toxoplasmosis is at high risk for *Pneumocystis* pneumonia based on her CD4 count. Although she describes a possible rash during prior treatment with trimethoprim-sulfamethoxazole, a rash limited to the elbows would be unusual for a drug reaction, and reactions to sulfamethoxazole, the component that appears to be most commonly responsible for reactions to trimethoprim-sulfamethoxazole, are rarely immediate or life-threatening. Thus therapy with a sulfa drug is not contraindicated, and the patient was started on pyrimethamine-sulfadiazine-leucovorin for treatment of toxoplasmosis. Pyrimethamine and sulfadiazine target the same enzymes as trimethoprim and sulfamethoxazole (dihydrofolate reductase and dihydropteroate synthase, respectively), and studies have shown that patients receiving pyrimethamine-sulfadiazine-leucovorin are at low risk for developing *Pneumocystis* pneumonia and thus do not require additional prophylaxis. While azithromycin prophylaxis should be started in this patient due to the low CD4 count, it has not been studied as an anti-*Pneumocystis* agent and thus additional prophylaxis for *Pneumocystis* would be required if it were indicated.

Ch / 342 MYCETOMA

1. All is true for eumycetoma *except* which one of the following?
 - A. The condition is most commonly found in tropical and subtropical regions.
 - B. Dissemination of subcutaneous lesion is common.
 - C. Examination of grains from draining sinuses can aid in identification of the offending fungus.
 - D. Local trauma and exposure to soil are typical initiating factors.

Answer: B Local trauma (e.g., wood splinters) introduces a mycetoma-causative fungus into the skin and subcutaneous tissues and initiates a chain of events that leads to chronic, suppurative granulomatous inflammation, tumefaction, and formation of multiple fistulous draining tracts in which fungal colonies in the form of grains are found. The color and morphologic characteristics of these grains could contribute to the identification of the offending fungal pathogen. Eumycetoma has a global distribution, but it is more common in areas with tropical or subtropical climate. Although extensive soft tissue involvement and adjacent bone involvement can be seen in advanced cases, visceral dissemination is typically absent (Estrada R, Chavez- Lopez G, Estrada-Chavez G, Lopez-Martinez R, Welsh O. Eumycetoma. *Clin Dermatol.* 2012;30:389-396).

2. Which antifungal has in vitro activity against *Scedosporium apiospermum* (*Pseudallescheria boydii*)?
 - A. Terbinafine
 - B. Fluconazole
 - C. Amphotericin B
 - D. Posaconazole
 - E. Ketoconazole

Answer: D *S. apiospermum* (*P. boydii*) is a cause of eumycetoma for which therapeutic options are limited because the fungus is resistant to most antifungals with the exception of the new triazoles, posaconazole and voriconazole (Negroni R, Tobon A, Bustamante B, et al. Posaconazole treatment of refractory eumycetoma and chromoblastomycosis. *Rev Inst Med Trop Sao Paulo.* 2005;47:339-346).

1. Which of the following organisms is most commonly associated with central nervous system infections?

- A. *Exserohilum rostratum*
- B. *Alternaria alternans*
- C. *Scedosporium prolificans*
- D. *Cladophialophora bantiana*
- E. *Exophiala* spp

Answer: D *Cladophialophora bantiana* is commonly associated with central nervous system infections, especially brain abscess, in normal hosts and in immunocompromised hosts. The other organisms frequently associated with central nervous system infections include *Ochroconis gallopavum* and *Rhinocladiella mackenziei*.

2. Which of the following organisms was associated with the U.S. epidemic involving injectable methylprednisolone acetate, leading to hundreds of cases of meningitis, parameningeal infections, and peripheral joint infections?

- A. *Exserohilum* spp
- B. *Alternaria* spp
- C. *Curvularia* spp
- D. *Bipolaris* spp
- E. *Fonsecaea* spp

Answer: A The major cause of the recently reported U.S. epidemic of contaminated methylprednisolone injections was *Exserohilum rostratum*. This organism was isolated by culture and/or polymerase chain reaction in the majority of patients in for whom positive tests results were available. The epidemic led to 751 proven and probable cases, of which approximately 8% died as a direct result of the infection.

3. Which of the following statement is *not* true concerning dematiaceous fungi?

- A. These organisms contain high concentrations of melanin in the cell wall.
- B. These organisms belong to the same class.
- C. These organisms are unusual causes of invasive human infection.
- D. These organisms are commonly found in the environment.
- E. More than 100 of these organisms have been associated with invasive human disease or colonization.

Answer: B These organisms belong to several classes of fungi. More than 100 dematiaceous fungi have been associated with human disease or colonization. These organisms are ubiquitous in the environment, and most have the capability to cause invasive disease in the appropriate clinical setting.

4. Which of the following features of chromomycosis is true?

- A. This disorder is characterized by discreet nodular skin and/or subcutaneous lesions.
- B. The infection often follows cutaneous inoculation through minor trauma.
- C. Most disease is caused by three organisms: *Fonsecaea*, *Cladosporium*, and *Phialophora*.
- D. The characteristic histologic findings are sclerotic cells or "copper pennies."
- E. All of the above are true.

Answer: E Chromomycosis is a disease largely seen in the tropics and follows minor skin trauma. The lesion is usually unilateral and is typically confined to an extremity. The lesions have a characteristic nodular, cutaneous, or subcutaneous appearance, and a histologic finding of sclerotic cells or copper pennies is characteristic of this condition. Chromomycosis is usually caused by one of the three organisms listed.

5. Which of the following is the best choice for therapy for chromomycosis?

- A. Fluconazole
- B. Amphotericin B
- C. Flucytosine
- D. Miconazole topical cream
- E. Itraconazole

Answer: E Among the choices given, itraconazole is the most effective agent. Among the azoles, posaconazole and voriconazole have excellent in vitro activity against most of the dematiaceous fungi, including those that cause chromomycosis. Small clinical trials evaluating these azoles and terbinafine suggest that each of these agents is effective when administered for an appropriate duration of treatment, usually months or even years.

Ch / 344 ANTIPARASITIC THERAPY

1. A regional health district in a resource limited area in rural Africa desires to treat school children empirically for intestinal helminthes to enhance their growth and intellectual development. Which of the following would be the best choice?

- A. Albendazole 400 mg once
- B. Ivermectin 150 µg/kg once
- C. Diethylcarbamazine 50 mg once
- E. Pyrantel pamoate 100 mg once
- F. Praziquantel 50 mg/kg once

Answer: A The most likely intestinal helminthes in areas of poor sanitation are *Ascaris lumbricoides*, hookworms, and *Trichuris trichiura*. A single dose of albendazole 400 mg is active against all of them. Ivermectin can be used against *Ascaris* and *Trichuris* but lacks activity against hook worms. Pyrantel pamoate has activity against *Ascaris* and hookworms, but not *Trichuris*. Diethylcarbamazine is used for the treatment of lymphatic filariasis. Praziquantel is used for the treatment of intestinal tapeworms (cestode) and most fluke (trematode) infections.

2. Plans are underway to start a new hospital in Southeast Asia where *Schistosoma japonicum*, *Fasciolopsis buski*, and *Clonorchis sinensis* are endemic. Which of the following antihelminthic medications should be available to treat these diseases?

- A. Nitazoxanide
- B. Praziquantel
- C. Albendazole
- D. Atovaquone/proguanil
- E. Tinidazole

Answer: B Praziquantel is the treatment of choice for these three pathogens and other flukes (trematodes) with the exception of *Fasciola hepatica*, the liver fluke. Nitazoxanide is indicated for intestinal protozoa, including *Giardia lamblia* and *Cryptosporidium*, and has activity against some intestinal nematodes and cestodes. Albendazole is used primarily for intestinal round worms and neurocysticercosis. Atovaquone/proguanil is effective for the prophylaxis and treatment of malaria. Tinidazole is used for the treatment of anaerobic luminal pathogens including *Entamoeba histolytica*, *Giardia lamblia*, and *Trichomonas vaginalis*.

3. A 24-year-old man is planning a 7-day trip to a game park in Tanzania, East Africa. He has a history of depression, which is well controlled with daily fluoxetine (Prozac). Which of the following would be the best choice for malaria prophylaxis?

- A. Mefloquine (Lariam) weekly
- B. Artemether/lumefantrine (Coartem) daily
- C. Chloroquine weekly
- D. Pyrimethamine daily
- E. Atovaquone/proguanil (Malarone) daily

Answer: E The options for prevention of chloroquine-resistant malaria include atovaquone/proguanil, doxycycline, mefloquine, and primaquine. They are of comparable efficacy. In respect to side effects, atovaquone/proguanil is the best tolerated. Artemether/lumefantrine and other artemisinin derivatives have short half-lives and cannot be used for prophylaxis. Chloroquine cannot be used in sub-Saharan Africa where chloroquine-resistant *Plasmodium falciparum* is endemic. Likewise, resistance to pyrimethamine is widespread in Africa. Mefloquine is effective against chloroquine-resistant malaria but is associated with serious neuropsychiatric and other effects, including depression, psychosis, and seizures.

4. A 55-year-old woman presented in May with fever and headache of 1 day's duration. She returned 7 days earlier from a 3-week trip to game parks in Tanzania, East Africa. She is otherwise in good health and taking no medications. She denies cough, sputum production, nausea, vomiting, diarrhea, dysuria, and skin rash. On examination, her temperature is 40° C, blood pressure is 120/85 mm Hg, heart rate is 120 beats per minute, and respiratory rate is 18 breaths per minute. She has no rash, her neck is supple, chest is clear to auscultation and percussion, and abdomen is soft and nontender with normal bowel sounds. The laboratory technician on call has never done a malaria smear, and the hospital does not offer rapid diagnostic tests. Results from a reference laboratory will be available in 24 hours. Which of the following would be the best course of action?

- A. Treat with mefloquine
- B. Treat if parasites are identified at the reference laboratory
- C. Treat with chloroquine
- D. Treat with artemether/lumefantrine (Coartem)
- E. Treat with doxycycline

Answer: D Fever in a returning traveler from Africa is malaria until proved otherwise! A delay in treatment can result in death, and therapy should not be delayed. The fastest acting drug for acute malaria is the fixed combination artemether/lumefantrine. Chloroquine cannot be used because of widespread chloroquine-resistant *Plasmodium falciparum* in East Africa. High-dose mefloquine has the risk for neurologic toxicity and would be used only if other antimalarial drugs were not available. Doxycycline does not act rapidly enough to be used alone for the treatment of acute malaria.

5. A 27-year-old woman presents with diarrhea of 3 weeks' duration. She recently returned after a 6-week visit to the Amazon Basin of South America. She stayed in local houses, drank tap water, and was an adventurous eater. She has had four to six loose stools a day, bloating, and intermittent abdominal crampy pain. On physical examination, her temperature is 37.0° C, blood pressure is 120/62 mm Hg, heart rate is 70 beats per minute, and respiratory rate is 12 breaths per minute. She is in no distress. The bowel sounds are normal. Her abdomen is soft, nontender, and without mass or hepatosplenomegaly. The rectal examination is normal. She is HIV negative. Stool tests are positive for cryptosporidial antigen and giardia antigen. What is the best choice for treatment?

- A. Nitazoxanide
- B. Tinidazole
- C. Metronidazole
- D. Albendazole
- E. Praziquantel

Answer: A Nitazoxanide is the only drug with activity against *Cryptosporidium* species, and it is also effective against *Giardia*. Tinidazole and metronidazole are active against luminal protozoa, including *Entamoeba histolytica*, *Giardia lamblia*, and some others, but not *Cryptosporidium*. Albendazole is

active against most intestinal nematodes. Although it has some activity against *Giardia*, albendazole is not the drug of choice for giardiasis and is not effective for *Cryptosporidium*. Praziquantel has activity against tapeworms (cestodes) and most flukes (trematodes), with the exception of *Fasciola hepatica*.

Ch / 345 **MALARIA**

1. A young American adult consults with you before travel to Kenya. Appropriate regimens for the prevention of malaria in travelers from a developed country to areas with chloroquine-resistant *P. falciparum* malaria include

- A. Malarone, mefloquine, or artemisinin.
- B. Malarone, mefloquine, or doxycycline.
- C. Coartem, Malarone, or doxycycline.
- D. quinine, artemisinin, or Fansidar.

Answer: B These three drugs are all listed as first-line regimens for the prevention of malaria in travelers. Artemisinin and artemisinin-based combination therapy (Coartem) are not appropriate because of the short half-lives of artemisinins. Quinine is not appropriate because of a short half-life and poor tolerability.

2. Reasons for the predilection for *P. falciparum* to cause severe malaria include all of the following except

- A. cytoadherence of *P. falciparum*-infected erythrocytes to vascular endothelium.
- B. infection of erythrocytes of all ages.
- C. a high prevalence of resistance to available antimalarial drugs.
- D. increasing pathogenicity with increasing age of the patient.

Answer: D Major contributors to the pathogenesis of *P. falciparum* malaria include cytoadherence of *P. falciparum*-infected erythrocytes to vascular endothelium, infection of erythrocytes of all ages, and high prevalence of resistance to available antimalarial drugs. *P. falciparum* malaria does not generally show increasing pathogenicity with increasing age. Rather, the disease is typically most severe in young children because of their lack of prior exposure to the pathogen and thus lack of antimalarial immunity and possibly other factors.

3. The region with the greatest morbidity and mortality from malaria in the world is

- A. Africa.
- B. Southeast Asia.
- C. South America.
- D. Oceania.
- E. the Middle East.

Answer: A The greatest morbidity and mortality from malaria is in Africa, likely because of many factors, including a preponderance of *P. falciparum* malaria, particularly competent anopheline mosquito vectors, and limited medical infrastructure.

4. The region with the most highly resistant malaria parasites in the world is:

- A. Africa
- B. Southeast Asia
- C. South America
- D. Oceania
- E. Middle East

Answer: B Explanation. The greatest prevalence of parasites resistant to available antimalarial drugs is in Southeast Asia. Resistance to chloroquine, antifolates, mefloquine, and quinine is seen in this area, and new data demonstrate decreasing efficacy of artemisinins, manifested as delayed clearance of parasites after treatment with artesunate or artemisinin-based combination therapies.

5. A child from Ghana is admitted with fever, altered consciousness, acute renal failure, and 7% parasitemia with *P. falciparum*. Severe malaria should be treated with:

- A. Oral artemisinin-based combination therapy
- B. Malarone or mefloquine
- C. Quinine or quinidine
- D. Intravenous artesunate, if available, and as a back-up intravenous quinine or quinidine

Answer: D The new international standard-of-care for the treatment of severe malaria is intravenous artesunate. Oral therapy should be avoided in very ill individuals. Intravenous quinine or quinidine is highly effective, but intravenous artesunate was superior to intravenous quinine in randomized trials of Asians and Africans with severe malaria.

Ch / 346 AFRICAN SLEEPING SICKNESS

1. Risk factors for sleeping sickness is/are

- a. tsetse fly bite.
- b. residence in urban areas of North Africa.
- c. rural areas of sub-Saharan Africa.
- d. a and c.
- e. a and b.

Answer: D African sleeping sickness is rare in urban areas or in North Africa. This vector-borne parasitic disease is transmitted to humans and animals by the bite of the tsetse fly.

2. Clinical presentation of sleeping sickness is/are

- a. chancre at site of bite.
- b. fever and headache.
- c. lymphadenopathy.
- d. a and c.
- e. a, b, and c.

Answer: E Sleeping sickness can present acutely with a chancre at the site of the bite, fever, headache, and lymphadenopathy.

3. Diagnostic test(s) of sleeping sickness is/are

- a. visualize parasite in chancre, node, or blood.
- b. polymerase chain reaction (PCR) on cerebrospinal fluid.
- c. serology.
- d. a and c.
- e. a, b, and c.

Answer: E Diagnosis of African sleeping sickness can be accomplished by visualizing the parasite by PCR and serology.

4. What drug is used to treat patients with stage 1 sleeping sickness caused by *T. b. gambiense*?

- a. Pentamidine
- b. Melarsoprol
- c. Eflornithine
- d. a and b
- e. a, b, and c

Answer: A Therapies with demonstrated effectiveness include melarsoprol, pentamidine, and eflornithine. For stage I disease, pentamidine is the treatment of choice.

5. East African sleeping sickness is

- a. more rapidly progressive than West African.
- b. characterized by severe fevers.
- c. commonly associated with lymphadenopathy.
- d. a and b.
- e. a, b, and c.

Answer: D East African sleeping sickness tends to be more severe and rapidly progressive, with intermittent fevers that resemble those seen in malaria. Unlike West African sleeping sickness, in which lymphadenopathy (often generalized) is common, lymphadenopathy is not typically associated with lymphadenopathy in East African sleeping sickness.

Ch / 347

CHAGAS DISEASE

1. Which of the following measures have been important over the past few decades in reducing the transmission of *Trypanosoma cruzi* (Chagas disease) in endemic countries?

- A. Improvement of housing conditions
- B. Identification and treatment of babies with congenital Chagas disease
- C. Spraying of insecticides in at-risk houses to eliminate insect vectors
- D. All of the above
- E. A and C

Answer: E Improvement of housing conditions and insecticide spraying, along with education of at-risk populations, all of which reduce contact with infected vectors, have been at the core of the successful programs that reduce transmission of *T. cruzi*. Programs focused on identifying and treating babies with congenital *T. cruzi*-infection have not been implemented widely and in any event would have relatively little effect on reducing transmission of the parasite.

2. In which of the following patients is chronic Chagas disease (*Trypanosoma cruzi* infection) likely to be the cause of the patient's signs and symptoms?

- A. A 56-year-old man from rural Brazil with early-onset dementia
- B. A 58-year-old Bolivian woman with abdominal pain caused by a small bowel obstruction
- C. A 62-year-old man with weight loss, hemoptysis, and anemia
- D. A 20-year-old Bolivian man with recurrent syncope and third-degree heart block and an ectopic ventricular pacer on ECG
- E. A 7-year-old child with intermittent diarrhea and eosinophilia

Answer: D In the endemic countries, particularly in Bolivia, where the overall prevalence is about 7%, chronic Chagas disease is a major cause of serious rhythm disturbances, heart block and sudden death among young people. The other options are unlikely because a link between Chagas disease and dementia has not been established; chronic Chagas disease is sometimes manifest as obstructive megacolon but not small bowel obstruction; weight loss, hemoptysis, and anemia are more suggestive

of tuberculosis than Chagas disease; and intermittent diarrhea and eosinophilia are not associated with chronic Chagas disease in patients of any age.

3. Which of the following Latin American countries has the lowest prevalence of Chagas disease?

- A. Bolivia
- B. Dominican Republic
- C. Colombia
- D. Argentina
- E. Ecuador

Answer: B Chagas disease is endemic in all the countries of Central and South America, as well as in Mexico. None of the Caribbean islands are endemic for Chagas disease. The only persons with Chagas disease in the Dominican Republic would be immigrants from the endemic countries, and thus the prevalence there would be quite low and far less than in the other countries listed where vector-borne transmission continues.

4. Which of the following statements is false?

- A. Of all the countries in which Chagas disease is endemic, Bolivia has the highest prevalence.
- B. Several hundred cases of transfusion transmission of Chagas disease were reported in the United States and Canada before the implementation of donor screening in 2007.
- C. Transfusion transmission of *Trypanosoma cruzi* (Chagas disease) has been largely eliminated in the endemic countries by serologic screening of blood donors.
- D. Highly accurate assays for diagnosing Chagas disease are available in the United States, Canada, and the endemic countries.
- E. *Trypanosoma cruzi* is widely distributed among wild mammals and insect vectors in the southern and southwestern United States.

Answer: B Before the implementation of blood donor screening for Chagas disease in the United States and Canada in 2007, only nine instances of transfusion transmission of the infection had been reported. The other statements are all true: Bolivia's Chagas disease prevalence of about 7% is the highest of all the endemic countries; To the credit of politicians and public health authorities in the endemic countries, and because of the availability of accurate serologic assays, transfusion transmission of Chagas disease is largely a thing of the past. Mexico is a notable exception to this achievement, however, because universal donor testing for Chagas disease has not been implemented there yet. To the surprise of many, in the southern third of the United States *T. cruzi* is widely enzootic in many species of wild mammals and insect vectors, as well as in domestic dogs.

5. The current consensus of experts in Chagas disease holds that the following groups of persons with *T. cruzi* infection should be given specific treatment (benznidazole or nifurtimox) except

- A. babies with congenital Chagas disease.
- B. patients older than 50 years of age with advanced symptomatic Chagas heart disease.
- C. children and adolescents up to age 18 years.
- D. patients with AIDS and reactivated acute *T. cruzi* infection.
- E. adults with acute Chagas disease and mild symptoms.

Answer: B A panel of experts in Chagas disease from the endemic countries as well as the United States and Canada, convened by the Centers for Disease Control and Prevention in 2006 with the goal of developing evidence-based guidance on diagnosis and treatment, concluded that all groups of patients listed above should be treated, with the exception of patients older than 50 years of age or those with advanced symptomatic Chagas cardiac disease (Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of Chagas disease in the United States: a systematic review. *JAMA*. 2007;298: 2171-2181).

1. A 60-year-old woman has been experiencing fever without chills for 10 days, starting 1 month after a 6-month travel from China to Europe. Clinical examination shows splenomegaly and liver enlargement. Laboratory parameters show anemia, leukopenia, and thrombocytopenia. Which of the following statements is correct?

- A. The most likely diagnostic possibilities are a hematologic condition and visceral leishmaniasis.
- B. The most likely diagnostic possibilities are bacterial infection and Chagas' disease.
- C. The most likely diagnostic possibilities are viral infection and histoplasmosis.
- D. None of the above is accurate.

Answer: A The association of fever and splenomegaly with pancytopenia is highly suggestive of but not specific for visceral leishmaniasis. Several hematologic conditions (myeloproliferative neoplasms, splenic lymphoma, Castleman's syndrome) are manifested with the same association of signs and laboratory abnormalities. Bacterial conditions and acute Chagas' disease are infrequently associated with pancytopenia, so this option is possible but less frequent. Viral infections (human immunodeficiency virus, human herpesvirus 8, cytomegalovirus) and histoplasmosis may be manifested with splenomegaly and pancytopenia, but these presentations are less prevalent in series of fever of unknown origin (at least in the European context), so this option is possible but less likely.

2. A 3-year-old child has fever, splenomegaly, anemia, leukopenia, and thrombocytopenia. Direct examination of a bone marrow aspirate (Giemsa-stained smear) for *Leishmania* amastigotes is negative. The most sensitive and specific, safest laboratory test to confirm the diagnosis of visceral leishmaniasis is

- A. Wait for *Leishmania* culture on the bone marrow aspirate to become positive
- B. Test for antileishmanial antibody
- C. Quantitative polymerase chain reaction (PCR) for *Leishmania* on a blood sample
- D. Direct examination of a splenic aspirate (Giemsa-stained smear)
- E. Direct examination of the bone marrow aspirate

Answer: C Quantitative PCR is a highly sensitive and specific test as soon as thresholds for symptomatic disease have been defined (low-grade positivity is frequent in endemic areas). Antileishmanial antibody can be positive because of past infection. Culture is also a sensitive test although generally less so than an optimized PCR based on the amplification of kinetoplastic DNA. Splenic aspiration is not a safe procedure.

3. A 22-year-old HIV-seropositive man with fever, splenomegaly, and pancytopenia has visceral leishmaniasis confirmed by quantitative PCR on a peripheral blood sample. The following items suggest a complicated form.

- A. Mucosal hemorrhages
- B. Presence of splenomegaly 5 cm below the costal margin
- C. Cough
- D. Moderate thrombocytopenia

Answer: A Hemorrhage and bacterial superinfection are the two main complications of advanced visceral leishmaniasis. Splenomegaly and mild to moderate thrombocytopenia are present in a majority of patients with uncomplicated visceral leishmaniasis. Dry cough is present in 10 to 15% of patients with visceral leishmaniasis (but will justify diagnostic study to rule out a bacterial superinfection in the lung).

4. A 2-year-old child has parasitologically confirmed, uncomplicated visceral leishmaniasis. The treatment option with the most favorable therapeutic window is
- A. Miltefosine 2.5 mg/kg for 28 days orally
 - B. Pentamidine mesylate 4 mg/kg for 10 days by slow IV infusion
 - C. Amphotericin B deoxycholate 0.5 mg/kg/day for 14 days by slow IV infusion
 - D. Meglumine antimoniate (pentavalent antimony) 20 mg SbV/kg/day for 28 days by slow IV infusion
 - E. Liposomal amphotericin B 10 mg/kg D1 and D2 by slow IV infusion

Answer: E All these options have been used in the therapy of visceral leishmaniasis. The 2-day schedule of liposomal amphotericin B has been validated in children.

5. A 35-year-old woman has a subacute, painless, crusted ulceration of the forearm that appeared 1 month after travel to Israel. Which of the following findings makes the diagnosis of cutaneous leishmaniasis unlikely?
- A. The lesion has an oval shape.
 - B. The lesion is infiltrated.
 - C. The lesion had a red, painful border for the last 4 days.
 - D. The lesion reached its maximum size in less than a week.
 - E. The lesion has small peripheral papules.

Answer: D Cutaneous leishmaniasis evolves subacutely, and therefore a lesion that reaches its maximum size within a week of its appearance makes the diagnosis unlikely. Firm, sharply defined lesions are characteristic, and numerous satellite papulopustules can occur. Although the uncomplicated lesions are “cold and painless,” superinfection can make them “hot and painful” with surrounding erythema.

Ch / 349 TOXOPLASMOSIS

1. Toxoplasmosis should be suspected in the following groups of patients.
- A. Only those who own cats
 - B. Only those who eat undercooked or raw meat
 - C. Those with clinical syndromes suggestive of toxoplasmosis regardless of their epidemiologic history
 - D. Those who own cats or eat undercooked or raw meat

Answer: C One of the greatest misconceptions in the care of patients in whom the diagnosis of toxoplasmosis should be entertained is the belief among clinicians that *Toxoplasma* infection should be suspected only in patients with epidemiologic risk factors. In all epidemiologic studies addressing risk factors for *Toxoplasma* infection, a risk factor could not be established in up to 50% of individuals with toxoplasmosis. Toxoplasmosis should be suspected on the basis of clinical manifestations and should not be excluded solely by the absence of epidemiologic risk factors. (See Epidemiology section.)

2. The diagnosis of lymphadenitis due to toxoplasmosis can be established by
- A. Amplification of *Toxoplasma* DNA from the affected lymph node tissue by the polymerase chain reaction (PCR)
 - B. Isolation of the *Toxoplasma* strain by inoculation of macerated lymph node tissue in the peritoneal cavity of mice in reference laboratories
 - C. Presence in lymph node biopsy specimen of a classic histologic triad: reactive follicular hyperplasia, irregular clusters of epithelioid histiocytes encroaching on the margins of the germinal centers, and focal distention of sinuses with monocytoid cells.
 - D. Presence in lymph node biopsy specimen of caseating and necrotizing granulomas

E. Microscopic examination of lymph node tissue with Wright-Giemsa stain to identify presence of tachyzoites or tissue cysts

Answer: C Toxoplasmic lymphadenitis can be diagnosed by the identification of this classic inflammatory response in the microscopic examination of lymph node tissue. This classic histologic triad (reactive follicular hyperplasia, irregular clusters of epithelioid histiocytes encroaching on or blurring the margins of the germinal centers, and focal distention of sinuses with monocytoïd cells) has not been observed in other diseases causing lymphadenitis. The diagnosis requires intact lymph node tissue (e.g., excisional lymph node biopsy) and cannot be made with the fine-needle aspiration of a lymph node. Toxoplasmic lymphadenitis typically does not result in formation of caseating or necrotizing granulomas. Attempts at identifying the presence of tachyzoites or tissue cysts by various stain methods, amplifying the parasite's DNA by PCR, or isolating the parasite in reference laboratories from lymph node tissue have all yielded negative results or have been successful in only a handful of case reports. The most effective approach to diagnosis of toxoplasmic lymphadenitis is by performing *Toxoplasma* serologic tests at a reference laboratory and, if indicated, lymph node excisional biopsy.

3. The definitive diagnosis of toxoplasmosis in hematopoietic cell, stem cell, or bone marrow transplant recipients can be made by the following methods, *except*

- A. Amplification of *Toxoplasma* DNA in cerebrospinal fluid by PCR in patients with encephalitis
- B. Amplification of *Toxoplasma* DNA in bronchoalveolar lavage fluid by PCR in patients with pneumonia
- C. Amplification of *Toxoplasma* DNA in vitreous fluid by PCR in patients with atypical retinal lesions
- D. Amplification of *Toxoplasma* DNA in peripheral blood by PCR in patients with fever of unknown origin
- E. Amplification of *Toxoplasma* DNA in brain tissue by PCR in patients with encephalitis

Answer: E PCR is the primary method for the diagnosis of toxoplasmosis in immunocompromised patients. A positive *Toxoplasma* PCR test result in cerebrospinal fluid, bronchoalveolar lavage fluid, vitreous fluid, and peripheral blood and other body fluids is diagnostic of toxoplasmic encephalitis, pneumonia, chorioretinitis, and dissemination, respectively, in these patients. Ideally, all immunocompromised patients should be tested for *Toxoplasma* IgG and IgM before they become immunosuppressed or as soon as the diagnosis of the underlying immunosuppressive disorder has been made because serologic testing is less reliable or not at all reliable once the patient is in a more advanced immunosuppressive state. The identification of patients at risk of toxoplasmosis is facilitated by the identification of those who are *Toxoplasma* IgG positive and should not be solely based on epidemiologic history because up to 50% of at-risk patients may be missed. (See Diagnosis section, Immunocompromised Patients, and Table 349-2.)

4. All pregnant women should be tested for *Toxoplasma* IgG and IgM as early as possible during gestation to determine whether they have an acute infection (positive *Toxoplasma* IgG/IgM confirmed with additional tests at a reference laboratory) or are at risk of acquiring an acute infection during gestation (negative *Toxoplasma* IgG/IgM). Those identified as having acute *Toxoplasma* infection or toxoplasmosis during pregnancy acquired before 18 weeks of gestation should be treated with the following drug.

- A. Spiramycin
- B. Pyrimethamine
- C. Sulfadiazine
- D. Folinic acid
- E. Clindamycin

Answer: A Spiramycin is the drug of choice during pregnancy in an attempt to prevent transmission of the parasite to the fetus. Spiramycin is not teratogenic and can be obtained at no cost in the United States through the Investigational New Drug (IND) process at the Food and Drug Administration (301-796-1600). Medical consultation with the Palo Alto Medical Foundation Toxoplasma Serology

Laboratory ([PAMF-TSL], Palo Alto, Calif; www.pamf.org/serology; 650-853-4828; toxolab@pamf.org) is required. If *Toxoplasma* infection was acquired after 18 weeks of gestation (when vertical transmission rates become significantly higher) or fetal infection is highly suspected (e.g., ultrasound abnormalities suggestive of congenital toxoplasmosis) or established (positive *Toxoplasma* PCR test result in amniotic fluid), the combination of pyrimethamine, sulfadiazine, and folinic acid is the treatment of choice. None of these drugs should be used alone. Clindamycin could theoretically replace sulfadiazine in patients with significant sulfa drug allergy. (See Treatment section and Table 349-3.)

Ch / 350 **CRYPTOSPORIDIOSIS**

1. *Cryptosporidium* infection

- A. May be asymptomatic but still impair a child's growth
- B. Produces solid protective immunity
- C. Is readily treated with broad-spectrum antimicrobial agents
- D. Is primarily a food-borne pathogen
- E. Can be diagnosed with an iodine stain for parasites

Answer: A Asymptomatic infections can impair growth, even without causing overt diarrheal symptoms. In fact, because they are more common, the total stunting impact of asymptomatic infections can exceed that of the symptomatic ones. Furthermore, recurrent infection is common, especially where water and environmental fecal contamination is often seen, and it is difficult to treat, especially in the immunocompromised host. Finally, diagnosis requires special acid-fast or fluorescence antibody staining, enzyme-linked immunosorbent assay, or polymerase chain reaction analysis as routine iodine stains for ova and parasites typically do not identify this protozoan parasite.

2. Cryptosporidiosis

- A. Usually causes bloody diarrhea in immunocompromised patients
- B. Cannot be spread by direct contact because it requires maturation outside the host
- C. Is a major cause of moderate to severe diarrhea in developing countries
- D. Does not cause relapsing disease
- E. Is an acute disease

Answer: C *Cryptosporidium* can cause severe, watery, cholera-like diarrhea in immunocompromised patients, such as patients with AIDS. Because the infectious dose is low and sporozoites develop into the mature oocysts in the infected host, they are infectious when shed in the feces (unlike *Cyclospora*, which do require maturation outside the host). In the recent GEMS study in seven sites in Africa and Asia, *Cryptosporidium* was second only to rotaviruses as an attributable cause of moderate to severe diarrhea that can often recur. (Kotloff KL, Nataro JP, Blackwelder WC, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries [the Global Enteric Multicenter Study, GEMS]: a prospective, case-control study. *Lancet*. 2013;382:209-222.)

3. The risk of acquiring *Cryptosporidium* infections is

- A. Reduced by chlorination of water
- B. Greater in immunocompromised patients
- C. Reduced by filters that remove particles larger than 6 µm
- D. Requires ingestion of more than 105 parasite oocysts
- E. Greater in adults

Answer: B *Cryptosporidium* is a hardy, chlorine-resistant oocyst that can be infectious with doses as low as 150 or fewer oocysts and probably even lower doses in immunocompromised individuals. It is also able to pass through common filters unless they are definitely smaller than 1-µm filter size.

4. The major outbreaks of cryptosporidiosis were associated with

- A. Ingestion of contaminated drinking water
- B. Ingestion of contaminated recreational water
- C. Exposure to infected animals
- D. Ingestion of contaminated food
- E. Contact with infected persons or animals

Answer: A *Cryptosporidium* infection is transmitted by the fecal-oral route and results from the ingestion of *Cryptosporidium* oocysts through the consumption of fecally contaminated food or water (drinking and recreational water) or through direct person-to-person or animal-to-person contact. The major outbreaks of cryptosporidiosis were associated with fecally contaminated drinking water.

5. Which of the following is true regarding the treatment or prevention of cryptosporidiosis?

- A. Nitazoxanide reduces the shedding of oocysts in immunocompetent hosts.
- B. Disinfection by chlorination prevents cryptosporidiosis.
- C. Nitazoxanide cures cryptosporidiosis in immunocompromised patients.
- D. Filtration is an efficient method to prevent cryptosporidiosis.
- E. Ozone and ultraviolet irradiation are not adequate to prevent cryptosporidiosis.

Answer: A Nitazoxanide has emerged as the drug of choice for treatment of cryptosporidiosis in immunocompetent children and adults. In immunocompromised patients, treatment or prevention with nitazoxanide shows no evidence of a reduction in the duration or frequency of diarrhea. Chlorination alone is ineffective against *Cryptosporidium* oocysts. Ultraviolet irradiation and ozone are effective in inactivating *Cryptosporidium* and *Giardia* cysts in water and can be used to prevent transmission of waterborne protozoa.

Ch / 351 GIARDIASIS

1. A 24-year-old woman spends 4 days in Cancun and within 2 days of return to the United States develops diarrhea consisting of multiple episodes per day of unformed stool. The patient is normally well but 2 years ago was diagnosed with giardiasis. As her symptoms are now similar, she seeks evaluation for it again. The health care provider orders a stool examination for ova and parasites. Which is the correct answer?

- A. Giardiasis is the likely diagnosis because the symptoms are similar.
- B. Ordering a stool examination for ova and parasites is the best way to establish the diagnosis for her symptoms.
- C. The diagnosis of giardiasis is unlikely.
- D. Amebiasis is more common than giardiasis in travelers to Mexico.
- E. None of the above

Answer: C Giardiasis is unlikely. First, the incubation period is too short for giardiasis, amebiasis, and other gastrointestinal parasites. Second, most diarrhea episodes of travelers to Mexico are due to bacterial infections (e.g., *Escherichia coli*, *Campylobacter*, and *Salmonella*). If she is sufficiently unwell, evaluation should also be directed at these causes or empirical antibiotic treatment considered. Unless giardiasis is confirmed, treatment should not be initiated for this.

2. A 25-year-old man developed diarrhea and weight loss. He was diagnosed with giardiasis after an evaluation for diarrhea that also included stool culture and testing for *Clostridium difficile*, as he has a history of chronic sinusitis that has been intermittently treated with antibiotics. He was treated for *Giardia* with metronidazole and initially responded. However, his symptoms have returned, and he has again been diagnosed with giardiasis. What is the most appropriate step in his evaluation?

- A. Repeat evaluation for *C. difficile*.
- B. Re-treat with a second course of metronidazole.
- C. The *Giardia* is resistant and should be tested for drug sensitivities.
- D. Order quantitative immunoglobulin levels.
- E. None of the above.

Answer: D The patient has recurrent giardiasis, weight loss, and chronic sinusitis, which is consistent with a diagnosis of common variable immunoglobulin deficiency. Giardiasis in these patients is difficult to treat and recurrent. Although his diarrhea could be due to several causes, *C. difficile* is not likely because it was not diagnosed initially and would not have occurred while the patient was taking metronidazole. Another course of treatment is not unreasonable, but in general, re-treatment with the same drug fails in this situation.

3. A mother of 2- and 7-year-old children develops severe diarrhea. Five weeks earlier, the family stayed at a campground over the weekend. There was supplied faucet water from a deep well that is protected from surface contamination. Three weeks before becoming ill, both children began attending a new daycare school for the summer. She has had two episodes of dehydration requiring fluid resuscitation. On evaluation, she is found to be infected with *Giardia*. The most likely source of her infection is

- A. The camping trip
- B. The faucet water
- C. Her children
- D. The water in the home
- E. None of the above

Answer: C In addition to the patient, both of her children were subsequently diagnosed with giardiasis. Frequently, the parents of young children are diagnosed, and infection is then traced to a child who is a carrier or only mildly symptomatic. The entire family may become infected. Surface water from lakes or streams during camping can be a source of exposure compared with a relatively secure water source, such as a faucet at park destinations. Given the possible sources for her infection, the daycare center is most likely.

4. A 45-year-old woman who was diagnosed with and treated successfully for symptomatic giardiasis 6 months ago now returns to your office complaining of listlessness, intermittent abdominal pains, and occasional loose stools. Which is the most likely diagnosis?

- A. Lactose intolerance
- B. Recurrent giardiasis
- C. Bacterial diarrhea
- D. Post-giardiasis irritable bowel syndrome

Answer: D Although the symptoms are vague and could be due to recurrent giardiasis, the more likely diagnosis is irritable bowel syndrome secondary to prior symptomatic giardiasis. Irritable bowel syndrome and fatigue were found to occur more frequently than in controls after a large epidemic of giardiasis in Bergen, Norway. Prior giardiasis does not preclude other causes of her symptoms, such as depression. Symptoms and findings of lactose intolerance due to shortening of villi is commonly found during and shortly after giardiasis but would not be expected to be present 6 months after infection.

5. A 10-year-old Filipino child who lives in a rural area of the Philippines is taking part in a study surveying children for enteric parasites. He is found to have *Giardia* in his stool but is asymptomatic and is well nourished. Which of the following is a reason for not treating this child?

- A. The child is likely to be reinfected in his home setting.
- B. Treatment of giardiasis in children is associated with severe adverse drug events.
- C. Treatment is usually unsuccessful in endemic settings.
- D. The child is too old for treatment to be helpful.

Answer: A Prevalence of *Giardia* infection can be 20% or more in cross-sectional studies from highly endemic regions. Many of these persons are asymptomatic, and reinfection after treatment can be common, particularly in young children. Although he could be treated, there is debate in the literature about the benefits of treatment of asymptomatic children who are likely to be reinfected.

Ch / 352 AMEBIASIS

1. Individuals at increased risk for amebiasis include all *but*

- A. Diabetics
- B. Pacific Islanders
- C. Men who have sex with men
- D. Residents of institutions for the mentally retarded
- E. Children in the developing world

Answer: A All of the other answers are risk factors for amebiasis, with children in low-income settings in the developing world at highest risk.

2. Which statement is *false* for the parasite *Entamoeba dispar*?

- A. It is as prevalent as *Entamoeba histolytica* worldwide.
- B. It is a cause of amebic colitis and liver abscess.
- C. It is more common than *E. histolytica* in North America.
- D. It is identical in appearance to *E. histolytica* on stool ova and parasite examination.
- E. It is fecal-orally transmitted.

Answer: B *E. dispar* is not known to cause disease and is more common in temperate climates than the identical-appearing *E. histolytica*.

3. Which statement is true for the diagnosis of intestinal amebiasis?

- A. Serology is positive acutely in more than 90% of cases.
- B. Test results for occult blood in stool are positive in most.
- C. Stool ova and parasite examination is sensitive and specific.
- D. *E. histolytica*-specific stool antigen detection test is more than 80% sensitive for the diagnosis.

Answer: D Stool ova and parasite examination is sensitive and specific. Serologic testing by indirect hemagglutination is positive during acute illness in no more than 70% of cases (but >90% in convalescence). Blood in the stool occurs in virtually all patients with amebic colitis, but stools do not have to be positive for occult blood in amebic diarrhea. The stool ova and parasite examination is neither sensitive nor specific for amebiasis.

4. Which statement is false about extraintestinal amebiasis?

- A. Amebic liver abscess is much more common in men than in women and rare in children.
- B. Amebic brain abscess is seen only in patients with amebic liver abscess.
- C. Amebic liver abscess can be treated without drainage in many cases.
- D. Bacterial superinfection of amebic liver abscess is common.

Answer: D For unclear reasons, bacterial superinfection of an amebic liver abscess is rare.

1. A 35-year-old woman presented to the emergency department in Toronto with a 2-day history of fever, headache, and malaise. She had just returned from spending 2 weeks during June on Nantucket Island. A 3-inch expanding circular rash was noted on one of her extremities, and she was diagnosed with acute Lyme disease and provided with a prescription for 100 mg of doxycycline, to be taken twice a day for 21 days. A month later, she presents again with fever, headache, chills, myalgia, and fatigue. She had not traveled again and works as a law clerk. Complete blood count demonstrates a hematocrit of 35, hemoglobin of 12, white blood cell count of 3000 (60% neutrophils, 35% lymphocytes, and 5% monocytes), and platelet count of 120,000; a blood smear is normal. What is the most likely cause of the recurrent symptoms?

- A. Epstein-Barr virus infection
- B. Human anaplasmosis
- C. Myelodysplastic syndrome
- D. Human ehrlichiosis
- E. Babesiosis

Answer: E Symptomatic Epstein-Barr virus infection is unlikely in a 35-year-old patient and usually is accompanied by lymphocytosis with atypical lymphocytes. Although thrombocytopenia or leukopenia may be seen with anaplasmosis and ehrlichiosis, these infections are susceptible to doxycycline and would have been adequately treated with the course prescribed for the Lyme disease.

Myelodysplastic syndrome typically is manifested with anemia and without fever. Treatment failure may rarely occur with acute Lyme disease, mostly as a result of poor compliance of the patient with therapy, but later manifestations of Lyme disease are more likely to be a monarticular arthritis or radiculopathy. Babesiosis may be coacquired with Lyme disease, but babesia are not susceptible to the tetracyclines. The negative blood smear is not unusual, and the severity of illness is not necessarily related to parasitemia. Thrombocytopenia and leukopenia may be evident in the absence of hematologic signs of anemia, particularly in early infection. Polymerase chain reaction will often be positive when blood smears are negative, given its greater sensitivity. Serology with a high anti-*Babesia* titer would provide evidence of infection if polymerase chain reaction is not performed, given that the patient was likely infected 6 weeks previously.

2. A 30-year-old biologist presented with a 3-week history of watery, nonbloody diarrhea with nausea and low-grade fever. He had previously been in good health and had returned 6 weeks ago from a field trip to Panama, where he had stayed for 1 month. He had several episodes of diarrhea in Panama that had responded quickly to Pepto-Bismol. He had remained hydrated and thus his activity was not curtailed. He now seeks medical attention because the diarrhea fails to respond to Pepto-Bismol or Imodium. Physical examination findings are normal, as is a complete blood count with the exception of slight eosinophilia. The patient admits to eating local foods and failing to always drink bottled water. Leukocytes are not noted in a stool examination, but Charcot-Leyden crystals are present. Stool analysis for ova and parasites demonstrates $30 \times 15\text{-}\mu\text{m}$ oocysts with a sharply defined cell wall and a single sporoblast. Rare *Entamoeba* spp cysts with eight nuclei are also found. Which of the following would provide the most critical information for case management?

- A. Testing for *Clostridium difficile* toxin
- B. Human immunodeficiency virus (HIV) infection status
- C. Testing for norovirus
- D. Specific identification of the *Entamoeba* sp
- E. Whether the Pepto-Bismol-treatable diarrhea was similar in quality to that experienced now

Answer: B The oocyst that was detected is likely *Cystoisospora belli*, which typically causes a self-limited diarrhea in immunocompetent younger patients. Norovirus and *C. difficile* disease should also terminate within a few days in a younger, healthy individual. The presence of eight nuclei identifies *Entamoeba coli*. Amebic infection reflects fecal-oral contamination, although the nonpathogenic *Escherichia coli* may also be found as a gut commensal. It is possible that the diarrhea episodes in

Panama were an uncomplicated traveler's diarrhea and that the current disease is not related. Persistent enteritis due to *C. belli* is commonly seen in HIV-infected patients, who may develop life-threatening persistent diarrhea, malabsorption, and dehydration and require lifelong suppression of *C. belli* with trimethoprim-sulfamethoxazole (Bactrim).

3. A 40-year-old married woman presents with a foul-smelling vaginal discharge of 3 days' duration. She is sexually active with her husband and complains of a recurring history of discharge during the last 6 months, typically a week after intercourse, but not with every instance of intercourse. The discharge would resolve within 2 weeks if she was abstinent. A wet mount of the discharge demonstrates flagellated cells moving with a tumbling motion, and a diagnosis of trichomoniasis is made. Metronidazole 250 mg orally three times a day is prescribed for 7 days. She returns 2 months later with the same discharge, stating that she had improved after the treatment course but that the discharge returned within the last week. Which of the following is the most likely explanation for the recurrence of symptoms?

- A. The patient's husband has *Trichomonas* infection and is reinfesting the patient.
- B. The patient has antibiotic-resistant trichomoniasis.
- C. The original diagnosis based on the wet mount examination alone was incorrect.
- D. The patient has been noncompliant with treatment.

Answer: A Patients may be reinfected by their untreated sexual partners, and thus a diagnosis of trichomoniasis should imply presumptive treatment of the partner. The majority of infected men are asymptomatic. The current Centers for Disease Control and Prevention recommendations for treatment failure are to re-treat with tinidazole. Metronidazole susceptibility may be established, but there is no guidance on minimum inhibitory concentration thresholds to define resistant strains. Although *Trichomonas vaginalis* is detected on wet mount examination of vaginal secretions in only about 60% of infected women, it confirms the diagnosis when it is seen in the appropriate clinical setting.

Ch / 354 CESTODES

1. Active cysts in the WHO Informal Working Group on Echinococcosis classification are

- A. CE1
- B. CE1, CE2
- C. CE3a, CE3b
- D. CE4
- E. CE4, CE5

Answer: B CE1 (unilocular) and CE2 (cysts with daughter cysts) are categorized as viable or active in the WHO Informal Working Group on Echinococcosis. When aspirated, viable protoscolices are found in the fluid.

2. The risk of lethal anaphylactic shock after an echinococcal cyst puncture is

- A. 2%
- B. 3%
- C. 4%
- D. 5%
- E. <1%

Answer: E In an analysis of the literature that included 5943 percutaneous puncture procedures of 5517 hepatic and nonhepatic echinococcal cysts, two cases of lethal anaphylaxis and 99 reversible anaphylactic reactions were reported. Lethal anaphylaxis occurred in 0.03% of percutaneous puncture

procedures, corresponding to 0.04% of treated cysts, whereas reversible allergic reactions complicated 1.7% of percutaneous punctures, corresponding to 1.8% of treated echinococcal cysts. Lethal anaphylaxis related to percutaneous treatment of cystic echinococcosis is an extremely rare event and is observed no more frequently than drug-related anaphylactic side effects are.

3. The best imaging technique for staging of cystic echinococcosis (CE) cysts of the liver is

- A. Computed tomography (CT)
- B. Magnetic resonance imaging (MRI)
- C. Ultrasound
- D. Positron emission tomography (PET) scan
- E. Scintigraphy

Answer: C Imaging plays the key role in diagnosis and staging of CE. The description of CE-specific imaging features and the WHO CE cyst classification are based on ultrasound. The reproducibility of the ultrasound-defined features of CE cysts is variable in MRI and CT. This is of particular importance for cysts that are not accessible by ultrasound and because of the increasing availability and overuse of CT and MRI.

A retrospective study was conducted in patients with abdominal CE cysts seen on ultrasound who had additional CT or MRI scans performed; it showed that MRI reproduces the ultrasound-defined features of CE better than CT does. If ultrasound cannot be performed because of cyst location or patient-specific reasons, MRI with heavily T2-weighted series is preferable to CT.

4. In a patient presenting with seizures and calcified cysticercosis with surrounding edema on MRI, the most appropriate therapy is

- A. Antiepileptic drugs alone
- B. Antiepileptic drugs and albendazole
- C. Antiepileptic drugs and prednisone
- D. Antiepileptic drugs, albendazole, and prednisone
- E. Placement of a ventriculoperitoneal shunt

Answer: A Patients with calcified lesions no longer have viable cysticerci and thus do not benefit from antiparasitic drugs. Prednisone may transiently decrease edema, but there is no evidence of clinical benefit, and steroid withdrawal has been associated with flares of disease.

5. In a patient presenting with multiple subarachnoid cysticerci complicated by basilar meningitis, which of the following approaches have been associated with the best outcomes?

- A. Treatment with a 2-week course of albendazole and dexamethasone
- B. Removal of the cysticerci by open craniotomy
- C. Treatment with prolonged courses of albendazole, dexamethasone, and methotrexate
- D. Neuroendoscopic removal of intraventricular cysticerci
- E. Cerebrospinal fluid diversion alone for hydrocephalus

Answer: C Subarachnoid neurocysticercosis responds poorly to the doses of albendazole used for parenchymal infection. Use of cerebrospinal fluid diversion alone carries a high case-fatality rate. The optimal approach includes prolonged courses of antiparasitic drugs along with anti-inflammatory treatment. Higher doses of albendazole, combinations of praziquantel and albendazole, and endoscopic debulking (removal of cysticerci in the basilar cistern, not just the ventricles) have also been reported as helpful.

Ch / 355 SCHISTOSOMIASIS (BILHARZIASIS)

1. A 20-year-old man was admitted with a fever (temperature of 39° C), abdominal pain, dyspnea, malaise, and weight loss of 30 pounds in the last 10 days. He has lived in Italy but traveled to areas endemic for *S. mansoni*, where he swam in a lagoon 4 weeks before the start of symptoms. A mild enlargement of the liver and spleen was noted on examination, and chest radiographs showed interstitial infiltrates. Schistosomiasis is suspected. Which of the following is the most appropriate test for diagnosis?

- A. Stool examination
- B. Urine examination
- C. Real-time polymerase chain reaction in stool
- D. Serologic test
- E. Rectal biopsy

Answer: D Egg deposition can be documented only up to 4 weeks after exposure. Although serologic tests do not rule out previous *S. mansoni* infection, the patient did not have history of previous exposure to *S. mansoni*, and therefore serology is the best test for the diagnosis of acute disease.

2. Which of the following statements is correct about human schistosomiasis?

- A. It may be prophylactically treated with praziquantel.
- B. Praziquantel is currently the treatment of choice.
- C. The combination of praziquantel and oxamniquine is recommended.
- D. There is no combination treatment available.
- E. Susceptibility or resistance to praziquantel has not been reported.

Answer: B Praziquantel has a poor prophylactic effect, which reduces its efficacy in areas of high transmission of *Schistosoma*. However, praziquantel is considered the drug of choice to treat schistosomiasis for its efficacy, low adverse events including severe adverse events, single oral dose, and competitive cost. There is a combination of praziquantel and artemisin derivatives that shows increased cure rates in schistosomiasis treatment.

Ch / 356 LIVER, INTESTINAL, AND LUNG FLUKE INFECTIONS

1. Hepatic *Fasciola* is acquired by ingestion of:

- A. Uncooked shellfish
- B. Watercress
- C. Fresh fish meat products
- D. Fresh fish
- E. All the above

Answer: B Hepatic *Fasciola* do not invade fish or meat. After invading freshwater snails, they leave as free-swimming cercaria that subsequently attach to watercress (as well as water lettuce, alfalfa, mint, parsley, or khat).

2. *Paragonimus* is acquired by ingestion of:

- A. Uncooked crab or crayfish
- B. Watercress and fresh fish meat products
- C. All the above

Answer: A *Paragonimus* emerges from the snail and invades the second intermediate host, a crustacean such as a crab or crayfish, where they encyst and become the infective stage for a mammalian host.

3. The treatment of choice for *O. viverrini* or clonorchiasis is:

- A. Albendazole
- B. Praziquantel
- C. Ivermectin
- D. Triclabendazole
- E. Emetina

Answer: B For *O. viverrini* or clonorchiasis, praziquantel regimens have been shown in several studies to have cure rates of 91 to 97% and 83 to 85%, respectively. Albendazole has poor activity. Ivermectin is effective for onchocerciasis and strongyloides. Triclabendazole is the drug for *Fasciola*, but it is second-line option here. Emetina is a parenteral drug that is useful only for *Fasciola* with high toxicity.

4. Cholangiocarcinoma is associated in Southeast Asia with chronic carriage of:

- A. *Fasciola hepatica*
- B. *Strongyloides*
- C. *Toxoplasma*
- D. *O. viverrini*
- E. *Taenia*

Answer: D Several studies in Thailand have demonstrated a strong association of *O. viverrini* with cholangiocarcinoma. *Fasciola hepatica* is associated with fibrosis but not cancer. *Strongyloides* produces hyperinfection but not cancer. *Toxoplasma* does not invade the biliary tract. *Taenia* is not associated with cancer.

5. A 33-year-old man presents with pleural effusion and eosinophilia. In the following weeks he developed a recurrent hemoptysis. The most likely diagnosis is:

- A. Tuberculosis
- B. Strongyloidiasis
- C. *Toxocara*
- D. *Fasciola hepatica*
- E. *Paragonimus*

Answer: E The typical clinical pattern for *Paragonimus* is the damaged lung, where hemoptysis and eosinophilia are the more common presentation. Evaluation of the sputum will be the key diagnostic test in this case. TB is the main differential diagnosis, but eosinophilia is not common in TB. Strongyloidiasis produces lung disease (migratory eosinophilic pneumonia) but is rarely associated with pleural effusion. *Toxocara* usually affects children and produces systemic disease with liver involvement; lung involvement is rare and hemoptysis even more so. *Fasciola hepatica* is associated with eosinophilia, but its typical presentation is a liver “abscess”-like or metastatic-like syndrome, and lung involvement with hemoptysis is rare.

1. A 21-year-old woman living in rural Indonesia is in her third trimester of pregnancy and is found to have severe microcytic anemia, with a hematocrit of only 19%. She denies vaginal bleeding but consistently has darkened stools that are positive when tested for occult blood. Blood laboratory testing is also remarkable for eosinophilia and low serum albumin concentration. Which of the following parasitic infections is the most likely to result in this syndrome?

- A. Enterobiasis
- B. Amoebiasis
- C. *Diphyllobothrium latum* infection

- D. Hookworm infection
- E. Strongyloidiasis.

Answer: D Intestinal blood loss is the principal clinical manifestation of hookworm infection, which can lead to iron deficiency and microcytic anemia. Pregnant women and children are at greater risk due to their higher iron needs. *Diphyllobothrium latum* infection is associated with development of megaloblastic anemia as a result of vitamin B12 deficiency and is thus associated with an elevated, rather than low, red blood cell mean corpuscular volume. Infection with *Enterobius vermicularis*, *Entamoeba histolytica*, or *Strongyloides stercoralis* is not usually associated with intestinal blood loss or iron deficiency.

2. A couple has just returned from their honeymoon in the Caribbean complaining of an intensely pruritic rash on their feet, buttocks, and legs. On examination, the rash consists of multiple raised, serpiginous red tracks. Most of their time was spent relaxing on a beach owned by the resort where they were staying. Which of the following is the most likely causative organism?

- A. *Dracunculus medinensis*
- B. *Ancylostoma duodenale*
- C. *Ancylostoma braziliense*
- D. *Strongyloides stercoralis*
- E. *Enterobius vermicularis*

Answer: C The description of the skin lesions is typical of cutaneous larva migrans. This syndrome is most commonly caused by penetration of the skin by the larvae of the dog or cat hookworms, *Ancylostoma caninum* or *Ancylostoma braziliense*. *Strongyloides stercoralis* also may cause a migrating serpiginous dermatologic rash known as larva currens, but it is found most commonly on the buttocks and lower back because the larvae that cause the tracks originate from the anus. *Dracunculus medinensis* results in a dramatic ulcerative, painful, nonmigratory skin lesion from which the adult female worm emerges to release eggs into the environment. Neither *Ancylostoma duodenale* nor *Enterobius vermicularis* produce rashes.

3. A 60-year-old male kidney transplant recipient from rural Eastern Kentucky is admitted to the hospital with a 14-day history of fever and profuse diarrhea. His medications include prednisone, tacrolimus, mycophenolate mofetil, and lisinopril. Laboratory examination is remarkable for a leukocyte count of 13,000/mm³, of which 25% are eosinophils. In the hospital, blood cultures are repeatedly positive for *Escherichia coli*. Besides treating the bacteremia with antibacterial therapy, which of the following medications is indicated to treat the most likely underlying predisposing parasitic infection?

- A. Pyrantel pamoate
- B. Ivermectin
- C. Praziquantel
- D. Mebendazole
- E. Metronidazole

Answer: B The patient's clinical picture is suggestive of disseminated strongyloidiasis. *Strongyloides stercoralis* is endemic in rural parts of Appalachia and infection can be maintained in a host for decades due to the autoinfection cycle of this parasite. Immunosuppression, particularly with corticosteroids, may lead to hyperinfection and dissemination of larvae to aberrant locations in the body. Enteric bacteria such as *E. coli* can be carried by the migrating larvae throughout the body, resulting in gram-negative sepsis, meningitis, and abscess formation. Ivermectin is the treatment of choice for strongyloidiasis. Although albendazole is a second-line therapy, mebendazole, also a benzimidazole, has poor oral bioavailability and would therefore not be an ideal choice. Pyrantel pamoate and praziquantel are anthelmintics but have poor activity against *S. stercoralis*.

4. A young boy who recently emigrated from Guatemala to the United States with his parents is brought by them to the emergency room because of lethargy and severe abdominal pain that has persisted for about 2 days. He is unable to walk due to the pain. On physical examination, he is afebrile; bowel sounds are absent, and there is significant diffuse abdominal tenderness that is more pronounced in the right lower quadrant. Radiographic studies suggest acute intestinal obstruction at the level of the ileum. How did this child become infected with the most likely causative organism?

- A. Drinking water contaminated with cysts
- B. Ingesting soil contaminated with embryonated eggs
- C. Walking barefoot outside, thus permitting larvae in contaminated soil to penetrate the skin
- D. Swimming in lakes that harbor snails and cercariae
- E. Eating insufficiently cooked meat infected with cysts

Answer: B Infection with *Ascaris lumbricoides* causing intestinal obstruction is the most likely diagnosis.

This nematode is a soil-transmitted helminth that to be infective to humans requires that eggs undergo a phase of development and embryonation in warm, moist soil. Infection results from ingestion of contaminated soil. Drinking contaminated water containing cysts is the means of transmission for protozoan organisms such as *Giardia intestinalis* and *Entamoeba histolytica*. Meat is the vehicle for *Taenia* tapeworm or *Trichinella spiralis* infections, skin exposure to water containing the intermediate snail host is the means of acquiring schistosomiasis, and skin contact with contaminated soil pertains to the transmission of hookworm or *Strongyloides stercoralis*.

5. A young boy in Kenya is taken to the doctor because of episodes of blood-streaked diarrhea, fever, and lower abdominal pain. Examination of a smear of his feces under the microscope reveals many oval eggs with bipolar plugs. Which of the following complications might occur if the child is not treated for the causative helminth?

- A. Obstruction of the duodenum
- B. Rectal prolapse
- C. Asthma-like symptoms
- D. Gram-negative meningitis
- E. Severe megaloblastic anemia

Answer: B Usually, light infections with the whipworm *Trichuris trichiura* are asymptomatic. However, heavy infections may produce symptoms that include those of dysentery, as in this child. Failure to treat with an anthelmintic could result in rectal prolapse due to the chronic straining induced by the sensation of rectal fullness caused by the presence of many whipworms in the rectum and colon. Although microcytic anemia may develop due to intestinal blood loss associated with *T. trichiura* infection, megaloblastic anemia resulting from vitamin B12 deficiency is associated with infection with the tapeworm *Diphyllobothrium latum*. *T. trichiura* is small and the adult worms are located in the large intestine, making obstruction of the duodenum unlikely. Also, whipworm has no pulmonary phase like *Ascaris lumbricoides* or hookworm and is therefore not associated with respiratory symptoms. Meningitis due to gram-negative bacilli is associated with disseminated strongyloidiasis but not with whipworm infection.

1. A 40-year-old woman from southern India has severe lymphedema of her right lower extremity and left breast. She has had this condition for at least a decade, and it is a common condition in her rural village. She now has difficulty going to work and is extremely embarrassed by her deformity to the point at which she tries not to venture outside of her home except at night. What is the most likely diagnosis?

- A. Lymphatic filariasis
- B. Loiasis
- C. Onchocerciasis
- D. Dracunculiasis
- E. Podoconiosis

Answer: A The most likely diagnosis is lymphatic filariasis due to chronic infection with *Wuchereria bancrofti*. Although loiasis, onchocerciasis, and dracunculiasis all have dermatologic manifestations, none result in chronic, irreversible lymphedema. *Loa loa* is associated with transient and migratory Calabar swellings that are hypersensitivity reactions to migrating adult worms; *Onchocerca volvulus* infection can result in generalized chronic dermatitis, and adult *Dracunculus medinensis* worms can rupture through intact skin from their location in the subcutaneous tissues to release eggs into the environment. Podoconiosis can result in chronic lymphedema due to irritant skin exposure to red clay, although this occurs mainly in the lower extremities, almost always starting in the foot.

2. A 28-year-old graduate student in physical anthropology has been experiencing unusual swellings over different parts of her body for the past 2 months. The swellings range in size from 5 to 15 cm and generally last 2 to 4 days before resolving; they are preceded by mild pain and intense pruritus that lasts a couple of hours. The field research for her dissertation is based on observational studies of gorillas in Gabon. A complete blood count is remarkable for very high eosinophilia (4000/mm³) and an unusual finding on the peripheral blood smear (collected at mid-day) that prompts an urgent page from the laboratory technologist. What is the most likely explanation of the phenomenon seen on the blood smear?

- A. Microfilaria of *Onchocerca volvulus*
- B. Microfilaria of *Wuchereria bancrofti*
- C. Promastigote of *Trypanosoma brucei gambiense*
- D. Larva of *Dracunculus medinensis*
- E. Microfilaria of *Loa loa*

Answer: E The skin manifestations are most likely Calabar swellings due to migrating adult *Loa loa* worms in the subcutaneous tissue. These are usually transient and are preceded by pain and pruritus. Loiasis is endemic in Gabon. *Onchocerca volvulus* is also endemic in this country and may result in subcutaneous nodules, although these are usually neither migratory nor transient. In addition, microfilariae of *O. volvulus* are visualized after exiting from skin snip specimens, whereas those of *Loa loa* are seen in blood. The microfilariae of *Wuchereria bancrofti*, which is endemic in Africa, are present in the blood, although their periodicity differs from that of *L. loa*. *W. bancrofti* microfilariae are best visualized in blood collected at night whereas those of *L. loa* are more likely to be seen in a sample collected during the day, preferably between 10 am and 2 pm. *Trypanosoma brucei*, the causative agent of African sleeping sickness, does not cause migratory skin swellings and is not associated with eosinophilia, although promastigotes can be observed on a Giemsa-stained blood smear. Finally, *Dracunculus medinensis* is associated with nonmotile skin lesions due to the adult female worm rupturing through subcutaneous tissue to the external environment to release larvae; however, no part of the life cycle occurs in the blood.

3. Within 2 weeks of eating jerky that he made from a cougar he shot while hunting, an Oklahoma man develops severe vomiting and diarrhea, followed 2 days later by a fever of 38.7° C, throbbing headache, and myalgias. After a few more days of continued symptoms, he seeks medical attention. His white blood cell count at presentation is 17,300/mm³, with 25% eosinophils. Which of the following laboratory tests would be most useful in making the correct diagnosis?

- A. Serum creatinine concentration
- B. Enzyme-linked immunosorbent assay (ELISA) for the suspected pathogen
- C. Examination of a Giemsa-stained blood smear using a light microscope
- D. Serum creatine kinase concentration
- E. Skin biopsy

Answer: D The most likely diagnosis is trichinellosis, probably due to *Trichinella nativa*. Infected individuals, especially those with myalgias and muscle tenderness, usually have elevated levels of serum creatine kinase, likely because *Trichinella* larvae invade striated muscle cells, inducing myositis. Unless the myositis is severe and rhabdomyolysis develops, associated renal dysfunction is rare. At this point in the disease process, seroconversion has likely not yet occurred, and, therefore, the ELISA for *Trichinella* would be negative. Larvae are not usually detectable in a stained blood smear or a skin biopsy, although nurse cells, which are striated muscle cells containing encysted larvae, can be visualized on muscle biopsy specimens.

4. A 7-year-old boy who has never traveled outside of North America develops decreased visual acuity in his right eye. Visible leukokoria is evident to his parents, which prompts a visit to their pediatrician, who consults an ophthalmologist. Fundoscopy reveals a single lesion of the retina. Assuming that his ocular condition is caused by a parasitic worm, which is the most likely means that this child became infected?

- A. Being bitten by an infected black fly
- B. Eating dirt while playing in a Boston public park
- C. Swimming in a lake containing snails
- D. Walking barefoot outside while visiting the family's summer cabin in rural West Virginia
- E. Eating ceviche while on a family vacation to Mexico.

Answer: B Although several nematode species have been associated with ocular manifestations in humans, *Toxocara canis* and *Toxocara cati* are the most common etiologies of ocular larva migrans and are found worldwide. Children who eat dirt because of pica are most at risk. Dogs and cats naturally harbor the adult parasitic worms, but humans—especially children—may become accidentally infected when embryonated eggs are ingested, even though humans are unsuitable hosts for maturation into adult worms. Retinal involvement occurs when excysted larvae penetrate the small intestine and disseminate throughout the body, including the eye. Due to the inflammatory response, visually distinguishing the condition in situ from a retinoblastoma or ocular tuberculosis can be challenging. *Onchocera volvulus*, which is transmitted by the bite of a *Simulium* black fly, can cause ocular lesions, but these are almost exclusively corneal. In addition, onchocerciasis is endemic now mostly in Africa. Skin exposure to fresh water containing certain species of snails is the means of acquiring schistosomiasis, which does not result in retinal manifestations. Nor does *Strongyloides stercoralis*, which is endemic in certain rural parts of Appalachia and is acquired through skin exposure to soil containing infective larvae.

5. A 35-year-old woman who has recently immigrated to the United States from Cameroon presents with chronic atrophic dermatitis and punctate keratitis. Laboratory investigations reveal a peripheral eosinophil count of 3500/mm³. Microfilaria are observed in the anterior chambers of both eyes on slit lamp examination. When considering management of this patient, which of the following antiparasitic medications should be contraindicated?

- A. Ivermectin
- B. Diethylcarbamazine (DEC)

- C. Albendazole
- D. Pyrantel pamoate
- E. Praziquantel

Answer: B This woman most likely has onchocerciasis due to chronic infection with *Onchocerca volvulus*, resulting in the typical skin and ocular manifestations. DEC should never be used for treatment of onchocerciasis because of frequent unacceptable hypersensitivity reactions to dying microfilariae, which can range from urticaria and angioedema to hypotension and death. Ivermectin is the treatment of choice for *O. volvulus*, whereas albendazole, pyrantel pamoate, and praziquantel are neither effective nor detrimental in this condition.

Ch / 359

ARTHROPODS AND LEECHES

1. Which of the following is *not* a mechanism by which arthropod venoms cause human injury?

- A. Neurotoxins
- B. Extracellular matrix enzymes
- C. Dermonecrotic reactions
- d. Chemical burns
- E. Anticoagulants

Answer: B Whereas snake venoms typically mediate tissue necrosis and extracellular matrix degradation via enzymes such as metalloproteases, hyaluronidase, and myotoxic phospholipase A₂, arthropods are not known to cause injury through these mechanisms. Causes of toxic injury by arthropods (see Table 359-4) include neurotoxins (e.g., Australian funnel web spiders, Brazilian wandering spiders, centipedes, widow spiders); dermonecrotic toxins (e.g., brown *Loxosceles* spiders, Pacific funnel web spiders); chemical burns (e.g., millipedes); and anticoagulants (centipedes, leeches, *Lonomia* caterpillars).

2. A 20-year-old college student presents to her student health service clinic with an intensely pruritic papulovesicular eruption of both lower legs. She and her three roommates had recently adopted a stray dog despite their crowded and cluttered apartment. Which of the following should be recommended for management?

- A. Treat with topical agents and machine wash clothes and bed linens at 60° C followed by heated drying
- B. Evaluate her for underlying inflammatory bowel disease
- C. Consult a veterinarian about agents for flea control
- D. Apply topical steroids and exterminate or wash and dry all bedding on a hot setting
- E. Search for offending agents in the seams of clothing and burn such clothes

Answer: C The patient most likely has flea bites from the stray dog. As in this case, flea bites tend to cluster on the lower legs and manifest as intensely pruritic papulovesicles. A veterinarian should be consulted about agents for flea control, including lufenuron and fipronil. The management in option A applies to scabies. The pruritic lesions of scabies have a predilection for involvement of the interdigital web spaces, wrists, anterior axillary folds, periumbilical skin, areolae in females, and penis and scrotum in males. Option B would be the approach to a patient with classic pyoderma gangrenosum, which usually occurs in the lower extremities. Pyoderma gangrenosum can be confused with brown recluse spider bites. Option E applies to the management of body lice; infestation with body lice produces a widespread dermatitis with widespread excoriations (that can be similar to those seen in scabies) and the diagnostic finding of bluish maculae cerulae (see Fig. 359-6). Bed bugs have become endemic and are increasingly recognized on college campuses, among other sites. Their bites are characteristically found on the face, neck, and arms, typically in strings of bites termed “breakfast, lunch, and dinner.” Option D would apply to bed bugs.

3. Which of the following pairings of vector and disease it causes is correct?

- A. *Aedes* mosquitoes and malaria
- B. Fleas and yellow fever
- C. Sandflies and bartonellosis
- D. Wood tick and rickettsial pox
- E. Tsetse flies and African trypanosomiasis

Answer: E Tsetse flies are vectors for African trypanosomiasis. Triatome bugs are vectors for American trypanosomiasis. *Aedes* mosquitoes are vectors for dengue and yellow fever; anopheline mosquitoes are the vectors for malaria. Fleas are vectors for bartonellosis and endemic typhus; *Aedes* mosquitoes are the vectors for yellow fever. Sandflies are vectors for leishmaniasis, not bartonellosis. Wood ticks are vectors for Rocky Mountain spotted fever (along with dog ticks and *Amblyomma americanum*. See Table 359-2.

Ch / 360 ANTIVIRAL THERAPY (NON-HIV)

1. A 47-year-old man who has sex with men recently was diagnosed with HIV (HIV RNA = 22,400 copies and CD4 = 70 cells/mL) and hepatitis B (hepatitis B surface antigen [HBsAg] positive). He was started on tenofovir, emtricitabine, and efavirenz with a good response (HIV viral load < 50 and CD4 = 220). Two months later, he now has developed several days of severe nausea and vomiting and is unable to keep his medications down. The patient recalls your counseling about the risks of developing HIV resistance with intermittent doses and stops all his medications. The nausea and vomiting resolve over the subsequent few days.

He is between jobs and has travel planned. Since he now feels well with the good control of his HIV, he decides to remain on a drug holiday. Seven weeks later he develops malaise and general weakness. Biochemical testing of his blood now reveals the following: total bilirubin, 7.7 mg/dL; alanine aminotransferase (ALT), 2157 U/L; aspartate aminotransferase (AST), 2693 U/L; and alkaline phosphatase (Alk-P), 137 U/L. Which of the following is most likely to be responsible for his current clinical condition?

- A. HIV
- B. Hepatitis B
- C. Hepatitis D
- D. Syphilis
- E. Herbal medications

Answer: B The patient's HIV regimen of tenofovir, emtricitabine, and efavirenz is also an effective treatment for hepatitis B. The withdrawal of medications during the drug holiday will lead to active HIV replication. Although moderate increases in AST and ALT can occur, fulminant hepatitis as described in this case is unusual. Severe acute exacerbations of hepatitis, including fatalities, have been reported in hepatitis B virus (HBV)-infected patients who stop anti-hepatitis B therapy. Hepatitis D, syphilis, or herbal medication can all cause an acute severe hepatitis but would be much less common than reactivated hepatitis B.

2. A 48-year-old man has HIV (CD4 560 and RNA 14,000) and hepatitis B (ALT 5 times the upper limit of normal and HBV DNA 35,000 IU/mL). Treatment for both HIV and HBV is recommended. However, the patient is concerned about drug toxicities. Because of his high CD4 count and relatively low HIV viral load, he does not want to begin treatment for HIV but is willing to be treated for HBV. Which of the following would be the most appropriate treatment?

- A. Tenofovir
- B. Entecavir
- C. Ribavirin
- D. PEG-interferon alfa-2a
- E. Emtricitabine

Answer: D With the elevated ALT and HBV DNA, treatment is needed for this patient's hepatitis B. Treatment may be initiated with any approved antiviral medications, but tenofovir, entecavir, or PEG-interferon alfa-2a are the generally preferred agents. Emtricitabine, lamivudine, and tenofovir have activity against both HIV and HBV, and monotherapy (for HBV) with these agents would likely lead to HIV resistance. Therefore, the most appropriate treatment is PEG-interferon. Ribavirin may be used with interferon for the treatment of hepatitis C, but it has no role in the treatment of hepatitis B.

3. A 44-year-old heterosexual man with chronic hepatitis C and asthma (on inhaled corticosteroids) has been treated with telaprevir, interferon, and ribavirin for 7 weeks with good virologic response (hepatitis C virus [HCV] RNA level is > 1000 IU/mL at week 4). He routinely engages in high-risk sexual activity and now presents with 3 days of fever and fatigue as well as 1 day of pain with swallowing. On examination, he is afebrile, he has no cutaneous rashes, but examination of his mouth shows patchy desquamation of his tongue. Which of the following is the most appropriate recommendation?

- A. This could be acute HIV, so an HIV viral load should be sent.
- B. This could be a severe drug reaction, so the telaprevir, interferon, and ribavirin should be stopped.
- C. This could be severe leukocytoclastic vasculitis from hepatitis C, so the patient should receive intravenous solumedrol.
- D. This could be mucocutaneous candidiasis, so the patient should receive fluconazole.
- E. This could be secondary syphilis, so the patient should receive benzathine penicillin.

Answer: B The patient is at risk for HIV and secondary syphilis, and both can both be associated with pharyngitis, myalgia, and a mucocutaneous rash. However, isolated oral involvement with frank desquamation would be very unusual for these diseases. Inhaled corticosteroids can cause oropharyngeal candidiasis, which would present with pharyngitis, dysphagia, and white mucosal plaques on examination, but desquamation of the mucosal membrane would be unusual. Hepatitis C is associated with leukocytoclastic vasculitis, usually with cutaneous findings. Telaprevir has been associated with both mild and severe dermatologic manifestations. Mild rashes can be treated with withdrawal of telaprevir. Desquamation of the tongue would suggest a more severe dermatologic reaction such as the Stevens-Johnson syndrome, which can present with mucosal desquamation before any cutaneous eruption. In this case, stopping telaprevir, interferon, and ribavirin would be the appropriate recommendation.

4. A 61-year-old man with severe chronic obstructive pulmonary disease (COPD) presents with a 36-hour history of fever, cough, myalgia, and mild shortness of breath. Rapid antigen assay from a throat swab is positive for influenza B. His current medications include tiotropium, prednisone 10 mg daily, and albuterol as needed. When advised of the diagnosis of influenza B, he asks for the least expensive medication because he recently lost his health insurance. Which of the following is the most appropriate treatment?

- A. Amantadine
- B. Rimantadine
- C. Oseltamivir
- D. Zanamivir
- E. No treatment is required

Answer: C Oseltamivir, which is active against influenza B and is well tolerated, is the appropriate treatment. The patient has influenza B. Because of his history of severe COPD, his influenza B should be treated. Amantadine and rimantadine are both available as generic medications, but all strains of influenza B are resistant to amantadine and rimantadine. Inhaled zanamivir powder can cause bronchospasm in patients with underlying asthma or COPD and would not be an appropriate treatment in this patient.

Ch / 362 **RESPIRATORY SYNCYTIAL VIRUS**

1. A 78-year-old woman with a history of chronic obstructive pulmonary disease (COPD) and heart failure presents to her physician 5 days after the New Year complaining of 3 days of nasal congestion, worsening cough, increased sputum, and increasing dyspnea. She has a temperature of 38.8° C and diffuse inspiratory and expiratory wheezing. Sao2 on 2 L/min nasal O2 is 90%. She received influenza vaccine 2 months ago but states that over the holidays she was with several family members, including young children, with the “flu.” Which is the optimal diagnostic test to identify respiratory syncytial virus (RSV) infection?

- A. Serology demonstrating a single high titer of serum immunoglobulin (Ig)G to RSV
- B. A rapid RSV antigen detection assay on a nasal swab or nasal wash specimen
- C. Viral culture of nasal swab or nasal wash specimen
- D. Reverse transcription–polymerase chain reaction (RT-PCR) of nasal swab or nasal wash specimen

Answer: D Adults with RSV have relatively high levels of serum and mucosal antibody and subsequently shed relatively low titers of virus compared with infants. Rapid antigen tests and culture are significantly less sensitive than RT-PCR. Although serology is highly sensitive in adults, both acute and convalescent samples are required, so this an impractical diagnostic method for clinical use.

2. A 42-year-old man with acute myeloid leukemia received an allogeneic stem cell transplant from his brother 20 days ago and now presents with nasal congestion and rhinorrhea. His white blood cell (WBC) count is 400/μL with a lymphocyte count of 50/μL. A nasal swab sample is positive for RSV by multiplex PCR. His lung examination is normal, and his chest radiograph is clear. Sao2 is 96% while breathing ambient air. Which one of the following statements is most accurate regarding this patient?

- A. Therapeutic intervention is never indicated for upper respiratory tract symptoms associated with RSV infection in such a patient.
- B. Palivizumab (an RSV neutralizing monoclonal antibody) infusion will clear the virus from the upper respiratory tract and hasten recovery.
- C. Progression of RSV infection to lower respiratory tract involvement is uncommon unless the lymphocyte count is less than 50/μL.
- D. In nonrandomized studies, administration of inhaled ribavirin is associated with a decreased risk of progression to lower respiratory tract disease
- E. The use of intravenous IgG infusion in combination with inhaled ribavirin has been proven to provide optimal outcomes.

Answer: D RSV infection in hematopoietic cell transplants recipients can be severe. Disease will progress to lower respiratory involvement in about 25% of such patients and carries a 20 to 40% mortality. Factors associated with progression include total body irradiation and low absolute lymphocyte counts (<100/μL). In one analysis, RSV did not progress in patients with lymphocyte counts above 1000/μL. Adequately sized studies of palivizumab treatment, given alone or in combination with ribavirin, have not been performed. An analysis of 288 immunocompromised subjects from one large center found that treatment with inhaled ribavirin was associated with decreased risk of disease progression.

3. A 56-year-old man with COPD on 2 liters/min of home O2 presents in February with a 3-day illness characterized by rhinitis, sore throat, increase in his daily cough, and change in color and amount of sputum production. He is afebrile and has a respiratory rate of 26 and pulse of 110. He is breathless and is wheezing on examination. His WBC count is 6700 with a normal differential, his chest radiograph is unchanged from prior films, and his Sao2 is 78% on 2 L/min O2, which is significantly below his baseline of 92%. He is admitted to the hospital and cautiously placed on 4 liters of nasal O2. A nasal swab is positive for RSV by RT-PCR, and his sputum Gram stain shows more than 25 WBCs per

high-power field, with mixed flora. In addition to standard hand hygiene, which of the following infection-prevention measures should be implemented?

- A. Use of gowns and gloves for all patient contact
- B. Isolation of the patient in a negative pressure room
- C. Use of gloves, gowns, and facemask for all contact
- D. None of the above
- E. All of the above

Answer: A RSV can persist on hard surfaces for several hours, so gowns and gloves should be used to prevent transmission. RSV is transmitted by large fomites, not by small-particle aerosol, so neither negative pressure nor masks are necessary to prevent transmission to health care workers or other patients.

4. A 24-year-old medical student is seen in the student health service for nasal congestion, mild sore throat, and wheezing in late July. She has a history of mild untreated asthma since childhood. A rapid antigen test for influenza A is negative, and a rapid antigen test for RSV is weakly positive. On examination, her lungs show expiratory wheezes but are otherwise clear. Three days earlier she returned from rural Thailand, where she had worked for 2 months in a family medicine clinic. Which of the following statements is most correct:

- A. The rapid antigen test for RSV is reliable and confirms RSV as the cause of her symptoms.
- B. RSV infection is uncommon in July, so the positive antigen test should be considered a false positive.
- C. RSV is the most common cause of asthma exacerbations in young adults, so the positive antigen test should be considered definitive.
- D. To confirm the diagnosis of RSV, an RT-PCR assay should be performed.

Answer: D The most reliable diagnostic assay for RSV in adults is RT-PCR. In adults, the rapid antigen test for RSV has poor sensitivity and cannot be considered definitive. July is atypical for RSV in the United States, but the student had recently traveled to a tropical area in which RSV can circulate throughout the year. Although RSV can cause exacerbations of asthma, rhinovirus is a much more common precipitant of asthma in older children and adults.

Ch / 363 PARAINFLUENZA VIRAL DISEASE

1. A 2-year-old girl presents to the emergency department with stridor and dyspnea of 4 hours' duration. Her parents relate that she has had about 3 days of preceding low-grade fever, coryza, and rhinorrhea. When she woke up this morning, her parents heard a barking cough coming from the child's room and noted that her breathing was progressively noisier on the way to the hospital. On physical examination, the child is not toxic appearing, but she is uncomfortable, with obvious inspiratory stridor and a raspy barking cough. Which represents the most likely diagnosis and most appropriate management plan?

- A. The child likely has community-acquired bacterial pneumonia; obtain a chest radiograph and administer oral antibiotics.
- B. The child likely has community-acquired viral pneumonia; obtain a chest radiograph but do not administer oral antibiotics.
- C. The child likely has epiglottitis; obtain a lateral neck radiograph, begin intravenous antibiotics, then secure the airway.
- D. The child likely has croup; keep her quiet by allowing her to stay in mother's lap, provide blow-by oxygen, administer oral dexamethasone, and observe for improvement.
- E. The child likely has croup; perform a careful pharyngeal examination in an attempt to visualize the epiglottis, provide oxygen by rebreather mask, and administer intramuscular dexamethasone and subcutaneous epinephrine.

Answer: D This child likely has mild to moderate croup, based on the history and physical examination findings of stridor but her nontoxic appearance. The best course is to keep her quiet in a comfortable setting such as her parent's lap, give her oxygen in the least intrusive manner (blow-by), and give oral dexamethasone 0.6 mg/kg. Oral dexamethasone can decrease symptoms, shorten the stay in the emergency department or hospital, and reduce the need for intubation. Stridor and barking cough are generally not associated with community-acquired bacterial pneumonia. Viral pneumonia with hPIV can accompany croup; but if so, dexamethasone and oxygen also would be appropriate. Epiglottitis should always be considered when examining a young child with respiratory distress, but these children tend to be more toxic in appearance; ideally the airway should be secured before performing radiographs, intravenous lines, and other procedures that might upset the child and provoke airway collapse.

2. The grandfather of the child in Question 1 underwent bone marrow transplantation for malignancy 4 weeks before the child became ill. She visited with him extensively at home a few days before she herself became ill. Now, 4 days after that contact, the grandfather is reporting fever, cough, dyspnea, and increased sputum production. His wife is concerned because he has not "looked this bad" since the transplantation was performed. Which statement best characterizes his illness?

- A. He likely has hPIV pneumonia, having acquired the infection from his granddaughter; he should be admitted to the hospital and treated with aerosolized or intravenous ribavirin and intravenous immunoglobulin in view of his high risk for mortality.
- B. He likely has acquired hPIV infection from his granddaughter but because adult airways are larger, he is unlikely to exhibit symptomatic croup; reassurance and continued monitoring at home will be sufficient.
- C. He likely has community-acquired pneumonia and should be given antibiotics.
- D. He likely has *Pneumocystis pneumonia* and should be hospitalized for intravenous trimethoprim-sulfamethoxazole. Further diagnostic studies are unnecessary and would be not be cost-effective.
- E. None of the above

Answer: A This adult is likely significantly immunocompromised (first 100 days after bone marrow transplantation) and has a 10 to 30% of mortality with hPIV infection. The incubation period of hPIV and the timing of the illness in the child are consistent with transmission. Although the efficacy of ribavirin and intravenous immunoglobulin have not been proven in randomized clinical trials, their use should be considered because of the severity of his illness and his high risk of mortality. Hospitalization is likely warranted, with oxygen and supportive care given at minimum. Although adults with hPIV infection do not generally present with croup, this immunocompromised patient's condition warrants an urgent medical visit, likely with subsequent hospitalization. Many other causes of respiratory infection are possible in the first 100 days following bone marrow transplantation, but administering antibiotics without considering the contact history or obtaining further diagnostic specimens would be inappropriate.

1. A 23-year-old woman who is 6 months pregnant presents with fever, increasing cough, and dyspnea of 4 days' duration during a known community outbreak of influenza. Physical examination shows T 39° C, P 110, R 25, Sao2 (room air) 92%, bibasilar crackles, 2/6 systolic murmur at left heart border, and 1+ pretibial edema bilaterally without cords or calf tenderness. Abdomen shows gravid uterus with normal fetal heart sounds. Nose swab is negative for influenza antigen by rapid test. WBC count is 4000 with 75% PMNs, 15% lymphs, and 10% monos. Chest radiograph shows patchy bilateral mid- and lower lung zone densities. Lower extremity ultrasound shows no evidence for deep venous

thrombosis. You administer oxygen, hospitalize her, request urgent maternal-fetal and pulmonary consultations, and in the meantime decide to start which of the following regimens:

- A. Antibiotics for community-acquired pneumonia (CAP), acetaminophen, and oral oseltamivir
- B. Antibiotics for CAP, acetaminophen, and systemic glucocorticoids
- C. Inhaled zanamivir and oral oseltamivir
- D. Oral oseltamivir, systemic corticosteroids
- E. Antibiotics for CAP, acetaminophen, and antitussives

Answer: A Pregnant women are at increased risk for complications of influenza, with their risk increasing across trimesters and extending into the early postpartum period. This patient appears to be rapidly deteriorating, with progression toward acute respiratory distress syndrome (ARDS) and requires urgent intervention. The negative rapid influenza antigen test and the delay in presentation from onset of symptoms should not dissuade empirical use of antiviral therapy. The possibility of bacterial coinfection mandates the use of antibiotics pending microbiological studies. The combined use of two neuraminidase inhibitors has not been shown to be superior to oseltamivir alone, and in one trial an inhaled zanamivir-oral oseltamivir regimen was inferior in uncomplicated influenza in adults. Systemic corticosteroids have not been associated with improved outcomes in severe influenza, and observational studies indicate an increased risk of secondary infections, other complications, and even mortality in patients with pandemic H1N1 pneumonia and/or ARDS.

2. A 55-year-old woman presents for routine follow-up in late November. Aside from moderate obesity (BMI 32) and long-term smoking of 1 2 pack per day, she has no recognized chronic medical conditions. She has refused influenza vaccines in the past, claiming egg allergies, and is often noncompliant with her scheduled visits. She reports experiencing tongue swelling after ingesting eggs. You advise:

- A. Intramuscular recombinant hemagglutinin vaccine
- B. Oral egg protein challenge in the office, followed by standard intramuscular vaccine
- C. Intranasal live-attenuated influenza vaccine
- D. Intradermal influenza vaccine
- E. Allergy consultation, followed by desensitization if necessary and standard intramuscular vaccine

Answer: A Standard inactivated vaccine, intradermal vaccine, and live-attenuated intranasal vaccine are all produced in eggs and contain egg proteins. The risk of anaphylactic egg allergy may be significant in this patient, and an allergy evaluation is one course of action. However, the influenza season may well begin shortly, and her history of missing appointments may indicate that this may be the only opportunity to immunize her in advance of the season. The recombinant vaccine is produced in insect cells and does not contain egg proteins.

3. A 60-year-old man who returned 2 days ago from a business trip to Shanghai presents to the emergency department with 3 days of fever, fatigue, and nonproductive cough in January. He denies sore throat or coryza but reports nausea. None of his travelling companions report illness. He recalls having walked through various marketplaces during his trip but does not recall seeing live poultry. His physical examination shows T 38.5° C, P 95, R 18, chest clear. A rapid antigen test is negative for influenza. After consultation with local public health authorities, you submit a nasopharyngeal swab for diagnostic testing, start oral oseltamivir, and hospitalize him for close observation. On the following day, the swab is reported negative for respiratory viruses, but he has developed worsening cough and respiratory distress, with Sao2 of 85% on a 5 L/min facemask. Chest radiographs show bilateral ground glass opacifications. WBC count is 3.0 with 10% lymphocytes; platelets 95,000; serum creatinine 1.2 mg/ dL. Electrocardiogram shows nonspecific ST-T wave changes; serum troponin is normal. Antibiotics are started, pulmonary consultation is requested, and he is intubated for mechanical ventilator support. Gram stain of a tracheal aspirate shows some PMNs but only rare bacterial forms. Reverse-transcription polymerase chain reaction (RT-PCR) on the aspirate is positive for influenza A. You decide to adjust his regimen by:

- A. Switching to intravenous zanamivir
- B. Doubling oral oseltamivir dose by nasogastric tube
- C. Adding inhaled zanamivir
- D. Adding amantadine
- E. Adding systemic glucocorticoids

Answer: A His recent travel history raises concern of avian H7N9 infection (also consistent with the paucity of upper respiratory symptoms and negative initial nasopharyngeal RT-PCR for influenza and other respiratory viruses), but other influenza A viruses including A(H1N1)pdm09 are also circulating, and the first case of avian H5N1 in North America occurred in a Canadian traveler returning from Beijing. The patient is rapidly progressing, with apparent viral pneumonia despite initial oseltamivir therapy. Although multiple conditions warrant consideration (e.g., secondary bacterial infection, pulmonary emboli, heart failure from infarct or myocarditis), there are also the concerns that oseltamivir may not be adequately absorbed in critically ill patients and that oseltamivir resistance can emerge rapidly. Limited data indicate that extemporaneous preparations of oral oseltamivir can be effectively administered by nasogastric tube in mechanically ventilated patients, but double doses of oseltamivir do not appear more effective than standard ones. Intravenous zanamivir provides reliable delivery of high drug levels and is active against most but not all oseltamivir-resistant variants. Amantadine is not active for currently circulating human influenza A viruses, avian H7N9, or most avian H5N1 viruses. The commercial formulation of inhaled zanamivir should not be used in mechanically ventilated patients.

Ch / 365 ADENOVIRUS DISEASES

1. In early October, a U.S. Army recruit in week 3 of his basic training exercises presents with a febrile respiratory illness consisting of minimally productive cough, fever, rhinorrhea, mild conjunctival injection, and cervical lymphadenopathy. A chest radiograph demonstrates bilateral scant infiltrates. Several other members of his troop have had a similar illness. He was appropriately vaccinated, including oral adenovirus vaccine. Which virus is likely the cause of this recruit's illness:

- A. Influenza A/H1N1
- B. Influenza A/H3N2
- C. Adenovirus 14
- D. Influenza B
- E. Rhinovirus

Answer: C Adenovirus 14. Adenovirus is the most common cause of respiratory viral infection among military recruits. Typical symptoms include minimally productive cough, fever, rhinorrhea, mild conjunctival injection, and cervical lymphadenopathy. Influenza typically occurs from late November until early March. Although rhinovirus also circulates during this season, it is unlikely to cause an infection as severe as described. Additionally, because recruits are now getting adenovirus live-attenuated vaccine that includes types 3 and 7, adenovirus type 14 has become a frequent cause of infection.

2. A 30-year-old woman presents to your office with conjunctivitis, edema of the eyelids, pain, lacrimation, and photophobia. What is the most likely information to discuss with the patient?

- A. The disease is likely caused by adenovirus 8, 19, or 37.
- B. Blurry vision is common and likely will require missing work.
- C. The problem will typically involve only one eye.
- D. The infection is contagious, so careful hand hygiene and not sharing anything that touches her eye is critical.
- E. All of the above

Answer: E All of the above. This is a case of epidemic keratoconjunctivitis (EKC). EKC typically is associated with a follicular conjunctivitis with edema of the eyelids, pain, lacrimation, and photophobia that develop after an 8- to 10-day incubation period. The hallmarks of the disease include significant pain and blurry vision that typically prevents patients from being able to work. Although bilateral disease has been described, involvement of a single eye is more typical. As symptoms improve over time, so will the vision, generally without any long-term effects on the eye or vision. The infection is highly contagious and can easily be spread to other members of the household or other patients if infection control is not fastidious.

3. An otherwise healthy 54-year-old woman presents to your office in July with a 3-day history of cough, nasal congestion, generalized malaise, fever, myalgias, tonsillitis, and cervical adenopathy. Her chest radiograph is normal. You perform a multiplex respiratory virus polymerase chain reaction (PCR), which returns positive for adenovirus. What do you recommend?

- A. Admission to the hospital for evaluation of fever
- B. A single dose of intravenous cidofovir (1 mg/kg)
- C. Moxifloxacin 400 mg daily for 7 days for prevention of bacterial superinfection
- D. Symptomatic treatment with cough drops and acetaminophen
- E. Report the case to the health department for contact tracing.

Answer: D Symptomatic treatment with cough drops and acetaminophen. This is a classic case of adenovirus upper respiratory tract infection. This infection is associated with cough, nasal congestion, generalized malaise, fever, myalgias, tonsillitis, and cervical adenopathy; if there is concomitant conjunctivitis, the syndrome is termed *pharyngoconjunctival fever*. The infection is clinically indistinguishable from other viral causes of upper respiratory tract infection. Infection will typically resolve over the course of several days, and symptomatic treatment is all that is indicated. This patient has no signs of lower tract disease (pneumonia on chest radiograph, shortness of breath), so more severe infection is unlikely.

Ch / 366 CORONAVIRUSES

1. Middle East respiratory syndrome (MERS) coronavirus may be diagnosed from which patient specimens?

- A. Respiratory tract specimen
- B. Serum
- C. Stool
- D. Urine
- E. All of the above

Answer: E Virus has been demonstrated to be detectable in all of these patient specimens. Although respiratory tract specimens are most important for diagnosis, specimens from additional sites may aid in the diagnosis of patients.

2. What statement is most true about common human coronaviruses (OC43, 229E, NL63, and HKU1)?

- A. Whenever a common human coronavirus is detected, there are associated severe clinical symptoms.
- B. Occasionally, common human coronaviruses are detected in individuals with mild or no clinical symptoms.
- C. All common colds are associated with common human coronaviruses.
- D. Common human coronaviruses have never been associated with croup or pneumonia.

Answer: B Human coronaviruses may be detected from clinical specimens from mildly ill or asymptomatic individuals. Human coronaviruses are only one cause of the common cold, and these viruses also have been associated with croup and pneumonia.

1. A 21-year-old man presents to your travel clinic complaining of fever to 104° F and rash. He returned 5 days ago from a 1-month trip to Indonesia, where he served in a remote village. He was scrupulous about taking his malaria prophylaxis but was bothered by many mosquito bites per day. His fever started 3 days ago and was accompanied by headache, runny nose, and watery eyes. The rash started on his trunk 2 days ago and is also evident on his upper extremities. He was vaccinated for measles, mumps, and rubella at age 1 and again at age 5. The most likely etiology of his fever and rash are:

- A. Measles
- B. Malaria
- C. Dengue
- D. Parvovirus B19
- E. Rubella

Answer: C Dengue is the most likely cause of this young man's illness. Dengue is spread by mosquitoes and is the most common arboviral infection in the world. There is no specific therapy, so treatment is supportive with analgesics, hydration, and antipyretics. Measles is not very likely because the patient had received two MMR vaccines, the onset of the rash was only 1 day into the fever, and the rash did not progress cephalocaudally. However, the presentation of measles can be altered in vaccinated people. Given the risk of transmission to other people, it would be prudent to send a serum specimen for measles IgM testing. Malaria is a less likely possibility because of the malaria prophylaxis, but malaria testing also would be recommended in this situation. Parvovirus B19 infection is unlikely because its rash typically follows the prodrome by approximately 1 week, as compared with 1 day in this patient. Rubella is unlikely because its fever is rarely above 38.5° C and the rash progresses cephalocaudally.

2. A 5-year-old girl presents to your office with a 5-day history of increasing fever, runny nose, mild photophobia, conjunctivitis, and a brassy cough. A rash that started on her face 2 days ago has now spread to her neck and upper torso. On physical examination, she has white plaques on an erythematous base on her buccal mucosa. Her lungs are clear, and her chest radiograph is consistent with a diffuse patchy bronchopneumonia. The most appropriate therapy to start is:

- A. Ceftriaxone
- B. Vitamin A, 200,000 IU/day for 2 days
- C. Azithromycin
- D. Antipyretics and symptomatic cough suppressant alone
- E. Ribavirin

Answer: B Although measles can present with a secondary bacterial pneumonia, it is common to have a viral pneumonia due to the measles virus. The absence of a consolidation on chest radiograph or abnormal lung findings on physical examination suggests a viral etiology. There is no indication for ceftriaxone or azithromycin. Vitamin A treatment of children with measles has been associated with decreased morbidity and mortality rates. The World Health Organization currently recommends two doses of vitamin A for all children with acute measles, regardless of their country of residence. Antipyretics, symptomatic cough suppressants, and analgesics are recommended for patients with uncomplicated measles. Although ribavirin has been demonstrated to offer modest benefits in a few small clinical trials, it is not recommended for treatment of measles.

3. A 33-year-old woman is admitted to the hospital on her fourth day of measles rash with a secondary bacterial pneumonia due to methicillin-resistant *Staphylococcus aureus* (MRSA). The most appropriate isolation precautions for this patient consist(s) of:

- A. Contact isolation precautions
- B. Airborne isolation precautions
- C. Droplet isolation precautions
- D. Contact and airborne isolation precautions
- E. Contact and droplet isolation precautions

Answer: D Patients with measles should be on airborne precautions for at least the first 4 days of rash. Immunocompromised patients may shed measles virus for extended periods and should remain on airborne precautions for the duration of their hospitalization for the acute illness. Contact precautions are necessary for MRSA.

4. A 35-year-old mother comes to your travel clinic in the United States with her healthy 9-month-old infant in anticipation of a leaving in 2 weeks for a trip to France. To reduce the risk of measles associated with international travel you recommend:

- A. No preventive measures are needed for measles for travel to Europe.
- B. Confirm the mother has received at least one dose of measles-containing vaccine. If not, give her a dose of measles, mumps, rubella vaccine. Give the infant immune globulin prophylaxis, followed by revaccination according to the routine schedule after return from the trip.
- C. Confirm the mother has received at least two doses of measles-containing vaccine. If not, give her a dose of measles, mumps, rubella vaccine. Vaccinate the infant with single-antigen measles vaccine, followed by revaccination according to the routine schedule after return from the trip.
- D. Confirm the mother has received at least two doses of measles-containing vaccine. If not, give her a dose of measles, mumps, rubella vaccine. Vaccinate the infant with measles, mumps, rubella vaccine, followed by revaccination according to the routine schedule after return from the trip.
- E. Give both the mother and the infant immune globulin prophylaxis, followed by revaccination of the infant according to the routine schedule after return from the trip.

Answer: D Measles remains endemic in many developed countries, and many of the measles cases imported into the United States originate in Europe, including U.S. residents returning from travel, as well as foreign visitors. For adults preparing for international travel, documented receipt of two doses of measles containing vaccine is recommended. Single-antigen measles vaccine is not available in the United States. Vaccination is preferred over immune globulin in infants as young as 6 months of age without contraindications. In infants younger than 6 months, immune globulin may be indicated.

5. A 28-year-old mother and her 4-month-old infant were exposed to measles in a daycare setting 2 days before coming into your office. The mother has a documented history of receiving two doses of measles vaccine, the last dose at age 6. How do you provide postexposure prophylaxis for this mother and child?

- A. Give the mother another dose of measles, mumps, rubella vaccine. Vaccinate the infant with single-antigen measles vaccine, followed by revaccination according to the routine schedule.
- B. No prophylaxis is necessary; the mother is considered immune with two doses of vaccine, and the infant is protected by maternal antibody.
- C. Give the infant immune globulin prophylaxis, and consider the mother immune with two doses of vaccine. Vaccinate the infant according to the routine schedule after 12 months of age.
- D. Give the mother immune globulin prophylaxis. Vaccinate the infant with measles, mumps, rubella vaccine, followed by revaccination according to the routine schedule.
- E. Give both the mother and the infant immune globulin prophylaxis, followed by revaccination of the infant according to the routine schedule.

Answer: C The mother should be considered immune because she has received two doses of vaccine. However, the amount of antibody she transfers to her infant is less than would be transferred by a mother who had measles disease. As a result, the infant may become susceptible to measles in the first 6 months of life, when the risk of severe measles is high. Immune globulin is recommended for postexposure prophylaxis; measles vaccine is not given before 6 months of age.

1. A 19-year-old college student presents with a 1-day history of fever, mild headache, and bilateral parotitis. She relates that she received all of the appropriate childhood vaccinations. After examining her, you suspect mumps. What is your best option for diagnostic testing?

- A. Collect urine for mumps virus culture.
- B. Collect throat swab for mumps virus culture.
- C. Collect throat swab for mumps virus polymerase chain reaction (PCR).
- D. Collect cerebrospinal fluid (CSF) for mumps virus PCR.
- E. Collect acute and convalescent sera for mumps immunoglobulin G (IgG) by enzyme-linked immunosorbent assay (ELISA).

Answer: C All of the suggested testing modalities could provide confirmation of the diagnosis of mumps. However, mumps viral culture may not be routinely available and is expensive. Real-time PCR is a rapid and very sensitive assay for detecting mumps RNA and has replaced viral culture in most situations. CSF is a suitable specimen for PCR, but there is no evidence for serious CNS involvement in this case; lumbar puncture is not indicated. Acute and convalescent sera (collected after an interval of 4 to 6 weeks) will provide a retrospective diagnosis. Serologic testing for mumps IgM would also be an acceptable diagnostic approach but may be negative very early in the clinical course.

2. A 62-year-old man who has been in good health calls your office for advice. His 15-year-old grandson visited his home 3 days ago and has now been diagnosed with mumps. Your patient grew up in the United States and relates that his mother told him that he never had mumps. He does not recall receiving a mumps vaccine. He has heard stories about mumps orchitis and is very concerned. What do you recommend?

- A. Administer measles-mumps-rubella vaccine (MMR) as soon as possible.
- B. Administer mumps hyperimmune globulin as soon as possible.
- C. Administer the mumps skin test.
- D. Send blood for mumps IgG serology.
- E. Send blood for mumps IgM serology.

Answer: D More than 90% of adults who grew up in the United States between 1957 and 1967 (when the mumps vaccine was introduced) are seropositive for mumps, so the probability that this man is susceptible to mumps is low. Because approximately 30% of mumps infections are asymptomatic, many adults are seropositive with no history of disease. His serologic status can be confirmed by testing for mumps IgG. Mumps IgM testing is appropriate for diagnosing acute mumps but not for determining mumps susceptibility. Mumps vaccine (or MMR) could be safely administered, but there are no data regarding the efficacy of postexposure immunization. Mumps hyperimmune globulin was used in the past as therapy for mumps orchitis, but it is no longer recommended or available. The mumps skin test is an unreliable indicator of mumps immune status, and the antigen is no longer widely available.

3. There is an ongoing outbreak of mumps in your community, primarily involving high school and college students. Several of your adult patients have requested that they be tested for mumps susceptibility because they do not recall having mumps and can provide no documentation of vaccination. Based on mumps IgG serologic results, you have identified a few patients who are seronegative and therefore susceptible to mumps. Which of the following patients should receive mumps vaccination?

- A. A 31-year-old man with type 1 diabetes mellitus, chronic kidney disease, and hypertension
- B. A 23-year-old man who was recently diagnosed with AIDS (CD4+ lymphocyte count = 41 cells per μL) and is receiving antiretroviral therapy
- C. A 36-year-old woman who recently emigrated from Central America, is pregnant (gestational age 20 weeks), and has a teenaged child at home

- D. A 55-year-old man who is 2 years status post–cardiac transplantation and is currently doing well on an antirejection regimen of mycophenolate, tacrolimus, and prednisone
- E. A 40-year-old woman who has had a flare of her sarcoidosis with pulmonary and CNS involvement and is on a prolonged corticosteroid taper and is currently taking prednisone 30 mg daily

Answer: A Mumps is a live-virus vaccine containing replication-competent virus. Its use is contraindicated in (1) pregnant women; (2) persons with primary or acquired immunodeficiency syndromes; (3) persons with hematologic or lymphoproliferative malignancies; (4) persons receiving systemic immunosuppressive therapy (including prednisone ≥ 20 mg/day or equivalent for ≥ 2 weeks); or (5) persons with allergies to any mumps vaccine components. Mumps immunization (using MMR) is recommended for children or adults who are infected with HIV and who do not have evidence of severe immunosuppression (defined as CD4 count < 200 lymphocytes/ μL or CD4 $< 15\%$). Diabetes mellitus is not a contraindication to vaccination.

Ch / 370 **CYTOMEGALOVIRUS, EPSTEIN-BARR VIRUS, AND SLOW VIRUS INFECTIONS OF THE CENTRAL NERVOUS SYSTEM**

1. Clues to the diagnosis of cytomegalovirus (CMV) encephalitis in an AIDS patient presenting with cognitive impairment include all but which one of the following?

- A. Profound immunosuppression (CD4 count < 100 cells/ μL)
- B. Ring-enhancing lesions in the white matter of the brain on magnetic resonance imaging (MRI)
- C. The presence of CMV retinitis characterized by cotton-wool spots and/or the presence of CMV pneumonitis.
- D. A polymorphonuclear preponderance in the cerebrospinal fluid (CSF)
- E. Progressive ventricular enlargement on brain computed tomography (CT) or MRI

Answer: B Ring-enhancing lesions are not a feature of CMV encephalitis. Brain imaging usually shows progressive increase in the size of the ventricles, as well as ependymal and meningeal enhancement. CMV encephalitis is one of the few viral encephalitides in which polymorphonuclear cells may predominate with the CSF pleocytosis. Evidence of widely disseminated CMV, such as pneumonitis and retinitis, is commonly seen in profoundly immunosuppressed patients in whom CMV encephalitis develops.

2. Which of the following disorders carries the highest risk for progressive multifocal leukoencephalopathy (PML)?

- A. Sarcoidosis
- B. Multiple sclerosis treated with natalizumab
- C. Chronic lymphocytic leukemia
- D. AIDS
- E. Small cell cancer of the lung

Answer: D Almost 1 in 20 individuals, particularly in the pre-HAART era, developed PML in association with HIV infection. This incidence dwarfs that of any other disorder, although the risk exceeds 1 in 100 in individuals who are JC virus antibody positive and whose multiple sclerosis has been treated with natalizumab for more than 2 years.

3. Which of the following is the most effective treatment for PML?

- A. Restoring the immune system by eliminating an offending therapeutic agent or treating HIV infection with antiretroviral therapy
- B. Cyclophosphamide
- C. Camptothecin
- D. Mefloquine
- E. Mirtazapine

Answer: A All of the drugs listed have been tried in the treatment of PML, but none has demonstrated a meaningful benefit in clinical studies. However, restoration of the immune system allows for the return of a robust JC virus-specific CD8 response in the central nervous system and may arrest the disease.

Ch 371 **PARVOVIRUS**

1. A 5-year-old is brought by her concerned parents because of sudden onset of a rash over her face and chest. The patient has no other complaints or physical findings. Her older sibling suffered the same symptoms, and a fifth disease “epidemic” has been publicized in the local school district. Which is the appropriate action?

- A. Order appropriate serologic tests for viruses that can cause rash, including measles, rubella, human herpesvirus 6, and parvovirus; then treat her accordingly.
- B. Reassure the child and family.
- C. Reassure the family, but recommend that the child not attend school until the rash clears.
- D. Test all family members for antibodies to parvovirus B19 and for the presence of virus by sensitive DNA assays.
- E. Assess for B19 DNA; if positive, administer a short course of immunoglobulin.

Answer: B Expensive and intrusive testing is to be avoided in the evaluation of acute parvovirus infection in children, who are almost always minimally symptomatic and will have an uncomplicated clinical course. Fifth disease frequently appears as an epidemic, often at 3-year intervals in a population. Further evaluation would be warranted only in the unlikely event of more serious symptoms in any family member. Because the cutaneous eruption occurs after the formation of antibodies to parvovirus, the child is no longer infectious and may attend school.

2. You follow an 18-year-old girl who has sickle cell disease with only occasional pain crises on hydroxyurea therapy. Her parents inform you that she is more tired than usual, unwilling to attend school, and sleeping much of the day. You are aware of an epidemic of fifth disease in the community. What is your response to the child’s parents?

- A. Reassure them that she is suffering from parvovirus infection, which is not a serious infection of childhood.
- B. Immediately hospitalize the child and administer human immunoglobulin in order to clear any active parvovirus infection.
- C. Recommend laboratory testing in the next few days, including a blood count and parvovirus B19 serology. If the hemoglobin is below normal, transfuse her; then if anti-B19 immunoglobulin G (IgG) is detected, administer immunoglobulin.
- D. Have the child seen that day to determine her hemoglobin level and reticulocyte count. If both are lower than expected, transfuse packed red blood cells.
- E. Ask the parents to be alert to new, worrisome complaints, either a skin rash or joint symptoms, that would then trigger a more extensive evaluation.

Answer: D The symptoms and setting are highly suggestive of transient aplastic crisis of sickle cell disease, in which marked worsening of anemia can be life-threatening. The child should be seen emergently; a low reticulocyte count establishes the diagnosis, and erythrocyte transfusion will alleviate the symptoms. In transient aplastic crisis, serology is not useful because specific IgG and IgM to parvovirus likely will not be detected. Viral levels of B19 would be expected to be very high. However, children with sickle cell disease mount normal responses to B19 antigens and will resolve the infection within a few days or a week, so immunoglobulin therapy is unnecessary.

3. A 38-year-old mother of three presents with a history of several weeks of severe joint pains and swelling, especially of her hands and knees, as well as morning stiffness and fatigue. She relates that two of her children had a rash a few weeks preceding her illness and that a community outbreak of parvovirus was suspected. On physical examination, she has mild swelling and marked tenderness over the proximal phalangeal joints, tenderness on palpation of her knees, but no cutaneous eruption. Laboratory screening is largely unrevealing, including normal blood counts and routine chemistries, sedimentation rate, antinuclear antibody, and rheumatoid factor. However, serologic testing for antibodies to B19 parvovirus shows a high level of anti-IgG and above normal IgM. What do you recommend?

- A. Reassure the patient that she likely has a self-limited illness and prescribe nonsteroidal anti-inflammatory drugs for symptom control.
- B. Perform polymerase chain reaction testing to detect B19 parvovirus; if the virus is detected, administer immunoglobulin.
- C. Perform an invasive evaluation—including arthroscopy, synovial biopsy, bone marrow biopsy, and cardiac imaging—to detect other evidence of parvovirus infection.
- D. Monitor serologic assays and perform B19 by gene amplification before deciding on therapy.
- E. Refer her to a specialist because there is insufficient evidence to link her symptoms to a parvovirus infection.

Answer: A Arthropathy after a parvovirus infection may be debilitating in an adult. The pattern of symptoms and joint involvement can mimic rheumatoid arthritis, but without synovial destruction. The diagnosis is clinical, and tissue sampling is not known to be helpful. The typical patient relates a convincing history of exposure, as for example to children with fifth disease, and the laboratory shows evidence of past infection without viremia. The pathophysiology is not well understood, but immunoglobulin is not indicated, nor has it been effective. In most patients, only symptomatic treatment is required, and gradual resolution without sequelae is expected.

4. A 23-year-old woman in the second trimester of pregnancy reports that her children were exposed to a parvovirus B19 outbreak at school and now show the “slapped cheek” rash. She feels well. What is your advice?

- A. Because parvovirus leads to early fetal loss, mid-trimester abortion, and congenital malformation, you should recommend early termination of the pregnancy.
- B. Watchful waiting for symptoms
- C. Intrauterine red blood cell transfusion
- D. Immunoglobulin injections
- E. Serologic testing and ultrasound

Answer: E Most women who are exposed to B19 during pregnancy do not become infected, and only a minority of those who are infected have adverse consequences in their fetuses. The most prudent approach is to determine whether infection has occurred by evidence of IgM antibody or IgG seroconversion; if infection is documented, the course of pregnancy should be followed with ultrasounds of the fetus. The mother will mount a neutralizing antibody response, so immunoglobulin is not necessary. Intrauterine transfusion is of uncertain benefit even to the hydropic fetus.

5. A 30-year-old man with severe anemia is found on screening to be HIV positive. Laboratory testing shows a very low reticulocyte count, and there are no erythroblasts on his bone marrow examination. He is seronegative for parvovirus B19. What therapy do you recommend?

- A. Blood transfusions
- B. Immunoglobulin therapy followed by highly active antiretroviral therapy
- C. Corticosteroids
- D. Thymectomy
- E. Highly active antiretroviral therapy

Answer: B Pure red cell aplasia in an HIV-infected individual is likely secondary to persistent parvovirus infection, and anemia may be the presenting manifestation of AIDS. In the absence of an adequate immune response, the virus infects red cell progenitors. Serology is often negative because of the absence of an immune response. However, the diagnosis can be established by detecting the virus itself in blood, where it should be abundant. This syndrome has become less prevalent in the era of highly active antiretroviral therapy, which is indicated in this patient. In addition, a course of immunoglobulin therapy is likely to clear the parvovirus and quickly resolve the pure red cell aplasia.

Ch / 372

SMALLPOX, MONKEYPOX, AND OTHER POXVIRUS INFECTIONS

1. A 24-year-old man presents to your office. He has a 2-cm nodular lesion on his right forearm. He does not appear systemically ill. He reports he was recently treated for malaria; he had a temperature of 103° F a week prior. He recently returned from work in Africa at a primate preserve in the Republic of Congo. Biopsy and electron micrographs of the lesion demonstrate poxvirus-particles. What is your diagnosis?

- A. Tanapox virus (*Yatapoxvirus* species)
- B. Monkeypox (*Orthopoxvirus* species)
- C. Myiasis
- D. Orf virus (*Parapoxvirus* species)
- E. Smallpox (*Orthopoxvirus variola*)

Answer: A The electron micrograph demonstrates poxvirus particles. These are of a characteristic size and shape that renders them distinguishable from herpesvirus particles and bacterial and parasitic particles. Tanapox virus infections typically present with high fever followed by the development of one or a few nodular lesions. The lesions are distinct from the classic vesiculopustular lesions of orthopoxvirus infections (such as cowpox, vaccinia, monkeypox, or smallpox). Monkeypox virus typically also causes lymphadenopathy. Myiasis is caused by the bot fly and could be found in a returning African traveller, but the electron micrograph would not be consistent with it. Pain would also be associated with the lesion. Orf lesions typically are not associated with a high-antecedent fever and are usually associated with exposure to a ruminant (commonly sheep or goat). Smallpox disease is typically a fulminant disease, with a more generalized vesiculopustular rash, especially in someone unlikely to have been previously vaccinated.

2. A 35-year-old woman is seen in the emergency department with an extensive pustular rash that covers more than 30% of her body. Lesions are apparent on the palms of her hands and soles of her feet. The distribution is centrifugal. The lesions are round and feel like buckshot. She is having difficulty swallowing because of pain. She has track marks on her arms. On further questioning, she reports “having the flu” 7 days ago, despite having received the flu vaccine 2 months prior. She reveals a history of illicit intravenous drug use and claims to use clean needles from the laboratory. She works as a clinical microbiologist in a virology laboratory that has an archival collection of materials. She has recently been characterizing various unknown historic clinical specimens to update the inventory. What would be your next step?

- A. Institute airborne precautions and call the health department.
- B. Take pictures of the lesions, get blood cultures, sample specimens and send for bacterial analysis, and start treatment for endocarditis.
- C. Perform a rapid plasma reagin test.
- D. Ask about her vaccination status.
- E. Get an infectious disease consult.

Answer: A The signs and symptoms are consistent with smallpox. Institution of airborne precautions will provide infection control and limit potential exposure to this patient. Notification of the health department will enable notification of the Centers for Disease Control and Prevention's Emergency Operations Center. A complete assessment of the patient can then ensue, using appropriate personnel protective equipment, ideally by a person previously vaccinated against smallpox.

3. A 25-year-old man reports to your office with a single vesiculopustular lesion on his forehead. He works on a farm with sheep and goats, none of which are ill. His wife is a laboratory postdoctoral fellow who works in a laboratory that studies monkeypox virus. You find out that she was recently vaccinated, 3 weeks ago, with smallpox vaccine before beginning work in the laboratory. What is the most likely cause of the forehead lesion?

- A. Vaccinia virus
- B. Orf virus
- C. Monkeypox virus
- D. Smallpox
- E. Pseudo cowpox

Answer: A Vaccinia virus is the live virus in smallpox vaccine. Although it is possible he could have a parapoxvirus infection acquired from the sheep or goats on the farm, none of the animals appears ill. Smallpox vaccine does not contain smallpox virus, which is the variola virus. The likely source of the vesiculopustular lesion is accidental implantation of vaccinia virus during close contact with his wife.

4. An epidemiology graduate student comes to your emergency department with a 5-day history of rash. The rash initially manifest as small red spots, which then became vesicular. She also notes painful adenopathy in her cervical and axillary lymph nodes. She describes a fever before the onset of the rash. She returned from Africa 1 week ago. On the plane, she had a fever. She had been working in the Democratic Republic of Congo (DRC) on maternal-fetal health issues of indigenous people in the equatorial region of the DRC. She has been living within the community and helping with all household and village activities. You suspect she may have monkeypox. What antiviral agent might you consider using if the diagnosis is confirmed?

- A. Brincidofovir or tecovirimat
- B. Acyclovir
- C. Ganciclovir
- D. Adefovir
- E. Stavudine

Answer: A Both brincidofovir (CMX-001), the orally bioavailable derivative of cidofovir, and tecovirimat (ST-246 or Arestyvyr) have activity against orthopoxvirus infections.

5. In the above case, what samples would you take for diagnosis?

- A. Rash lesions and sera
- B. Blood culture
- C. Serum chemistries
- D. Complete blood count
- E. Thick and thin smears

Answer: A Poxvirus infections are usually identified by evaluation of material from the rash lesion itself. Polymerase chain reaction and culture can identify and characterize the virus. Electron microscopy can also help to exclude a herpesvirus infection. Serology can be useful if the rash lesions have resolved.

1. A 24-year-old woman comes into a university health service for counseling. She has become romantically involved with a 25-year-old man and is contemplating the initiation of a sexual relationship but is afraid to do so because he has genital warts and she has heard that human papillomavirus (HPV) is an incurable infection. She received three doses of the quadrivalent HPV vaccine 5 years ago and wants to know if her potential partner can be tested to determine whether she is protected against the HPV type with which he is infected. Which of the following is the most appropriate recommendation?

- A. Her partner should come to the health service for assessment and treatment of his warts and typing of his HPV. If it is a type that is included in the HPV vaccine, sexual activity is safe.
- B. Both she and her partner should be vaccinated, after which sexual activity would be safe.
- C. She should avoid vaginal intercourse but can safely engage in oral sex.
- D. Her partner should come to the health service for assessment and treatment of his warts but not testing. Sexual activity would then be safe with condoms.
- E. She should be tested to determine whether she has protective levels of immunity to see if sexual activity would be safe.

Answer: D It is highly likely that her potential partner's warts are caused by HPV 6 or 11, both of which are included in the quadrivalent vaccine and against which she likely has a very high level of protection. Tests to provide specific typing information on HPV-related lesions or levels of HPV-antibody are not commercially available or recommended. In addition to vaccine, lesion treatment and condom use can further reduce the risk for transmission. Booster doses of HPV vaccine are not currently recommended, and the vaccine does not have therapeutic benefit against existing infection. Genital HPV can be transmitted by oral-genital sex, although oral warts occur only infrequently. See Veldhuizen NJ, Snijders PJF, Reiss P. Factors affecting transmission of mucosal papillomaviruses. *Lancet Infect Dis.* 2010;10:862-874; and Workowski KA; Centers for Disease Control and Prevention. Sexually transmitted disease treatment guidelines 2014. *MMWR Morb Mortal Wkly Rep.* 2014 (in press).

2. A 28-year-old woman presents with genital bumps 6 weeks after a brief sexual encounter while on vacation. The lesions are slightly itchy but are otherwise asymptomatic. She is concerned that this represents a recurrence of a prior episode of genital warts and would like to refill a prescription for imiquimod cream. Her physical examination is notable for moist bilateral condylomatous lesions on her labia minora and bilateral nontender inguinal lymphadenopathy. Which of the following would be the most appropriate diagnostic test?

- A. A skin biopsy of the lesion
- B. A blood test for syphilis
- C. A swab of the lesion for HPV testing
- D. A Pap test and an HPV co-test of her cervix
- E. It would be most cost-effective not to perform any test, but an empirical course of imiquimod should be initiated.

Answer: B Although a skin biopsy is the definitive method for diagnosing genital lesions, such as suspected warts, genital warts can often be diagnosed by clinical examination without diagnostic testing. In this case, the clinical presentation (moist bilateral painless lesions with nontender lymphadenopathy) would be suspicious for the condyloma lata lesions of secondary syphilis, which can be easily diagnosed by a serologic test for syphilis; empirical treatment without such a test could delay appropriate treatment. HPV testing is recommended only as part of cervical cancer screening, not to diagnose a lesion. Cervical cancer screening would not help to assess her clinical presentation, and HPV co-testing is not recommended for women younger than 30 years because of its poor specificity. See Workowski KA; Centers for Disease Control and Prevention. Sexually transmitted disease treatment guidelines 2014. *MMWR Morb Mortal Wkly Rep.* 2014 (in press).

3. You have recommended a quadrivalent HPV vaccine for a 17-year-old bisexual man visiting your adolescent health clinic. He has read that this vaccine, like many others, can have serious side effects and wants to know why this vaccine might be beneficial for him to receive. Which of the following is *not* a potential benefit of HPV vaccine for him?

- A. Prevention of genital warts
- B. Prevention of cervical cancer in a future female partner
- C. Prevention of plantar warts
- D. Prevention of anal cancer
- E. Prevention of oropharyngeal cancer

Answer: C The quadrivalent HPV vaccine is highly effective in preventing anogenital lesions due to the four HPV types contained in the vaccine (types 6/11, which commonly cause genital warts, and types 16/18, which cause a variety of types of genital and anal cancer). The vaccine is recommended in the United States for all males because of its benefit in preventing genital warts, anal intraepithelial neoplasia, and probably anal cancer. Preventing infection in young males has the potential to reduce the chance of infection in their future sexual partners, a phenomenon that has already been demonstrated for vaccinated females. Because HPV types 16/18 are also a cause of oropharyngeal cancer, the vaccine could potentially provide benefit in preventing this outcome as well. Plantar warts are generally caused by HPV 1 and other nongenital types, and the vaccine has no potential for preventing these lesions. See Bosch FX, Broker TR, Forman D, et al. Comprehensive control of human papillomavirus infections and related diseases. *Vaccine*. 2013;31S:H1-31.

4. HPV molecular testing is recommended in which of following clinical situations?

- A. Combined with a Pap test to screen for cervical cancer in a 35-year-old woman
- B. Screening for oral cancer in a 50-year-old man
- C. Combined with a Pap test to screen for cervical cancer in a 26-year-old woman who had previously received the HPV vaccine
- D. Combined with a Pap test to screen for cervical cancer in a 22-year-old woman
- E. Screening for anal cancer in a 45-year-old man who has sex with men

Answer: A The explosion of knowledge regarding HPV and its role in a variety of cancers has led to great interest in the use of molecular tests for screening and diagnosis. Testing is currently recommended only in limited circumstances, specifically for cervical cancer screening in combination with a Pap test for women 30 years of age or older and for triage of women with cytologic findings of atypical squamous cells of undetermined significance. Because of the higher prevalence of HPV in women younger than 30 years, HPV testing is not recommended for screening owing to its low specificity for detecting significant cervical lesions; prior vaccination status does not affect this recommendation. There are no data to support the use of HPV testing in screening for cancer at sites other than the cervix. See Bosch FX, Broker TR, Forman D, et al. Comprehensive control of human papillomavirus infections and related diseases. *Vaccine*. 2013;31S:H1-31; Schiffman MH, Solomon D. Cervical cancer screening with human papillomavirus and cytologic co-testing. *N Engl J Med*. 2013;369: 2324-2331; and Workowski KA; Centers for Disease Control and Prevention. Sexually transmitted disease treatment guidelines 2014. *MMWR Morb Mortal Wkly Rep*. 2014 (in press).

5. A 45-year-old HIV-infected man recently saw a news report that warned about HPV-related health issues in HIV infected men. He now comes to you for counseling. In considering how to address his concerns, all of the following are true except which of the following?

- A. HIV-infected persons are at increased risk for cervical and anal cancer.
- B. HPV-related lesions are more difficult to treat in HIV-infected persons.
- C. HPV may increase the risk that HIV-uninfected persons will acquire HIV.
- D. Cancer screening with anal Pap tests has been proved to prevent anal cancer in HIV-infected men who have sex with men.
- E. Although its protective benefit is unproved, HPV vaccines can be safely given to HIV-infected persons.

Answer: D Although cancers of both the cervix and anus occur with increased frequency in HIV-infected persons, cytologic screening has not been proved to prevent anal cancer and is not a recommended prevention strategy. Like many infections controlled by cell-mediated immunity, HPV infections are more common and difficult to treat in HIV-infected persons, especially those with advanced immunodeficiency. Although there is no proven benefit of HPV immunization in HIV-infected persons, there are no safety risks because the vaccine contains no live virus. Recent data indicate that HPV infection can increase the risk for HIV transmission, analogous to what is observed for many other sexually transmitted infections. See Denny LA, Franceschi S, de Sanjose S, et al. Human papillomavirus, human immunodeficiency virus, and immunosuppression. *Vaccine*. 2012;30S:F168-F174; and Workowski KA; Centers for Disease Control and Prevention. Sexually transmitted disease treatment guidelines 2014. *MMWR Morb Mortal Wkly Rep*. 2014 (in press).

Ch / 374 HERPES SIMPLEX VIRUS INFECTIONS

1. A 55-year-old woman presents in the emergency department with fever, expressive aphasia, and altered behavior during the month of September. Her husband reports that the symptoms began approximately 6 hours before presentation. She is an avid hiker and spelunker. Her physical examination, aside from fever and expressive aphasia, is otherwise normal. Her cerebrospinal fluid findings are as follows: protein 75 mg/dL, 36 white blood cells (equally divided between lymphocytes and neutrophils), 0 red blood cells, and a normal glucose level. A computed tomographic scan of her head is normal. Which of the following is the most likely cause of her illness?

- A. Enterovirus encephalitis
- B. Rabies
- C. Acute HIV infection
- D. Herpes simplex virus
- E. West Nile virus

Answer: D This is a classic presentation of a focal encephalopathic illness that is characteristic of herpes simplex virus encephalitis. Expressive aphasia and altered behavior are key to the diagnosis. About 20% of patients will not have red blood cells in their cerebrospinal fluid. Enterovirus very rarely causes a focal encephalopathic process; and when it does, it is in children. Rabies involves the cerebellum, whereas West Nile virus presents with anterior horn motor disease without altered behavior or expressive aphasia. Acute HIV encephalitis is a diffuse symmetrical encephalitis.

2. You elect to perform diagnostic studies on the aforementioned patient in order to determine the best management. Which of the following is most likely to confirm the diagnosis?

- A. A serum immunoglobulin M (IgM) level
- B. An electroencephalogram
- C. A serum IgG (acute and convalescent) level
- D. Biopsy of the nape of the neck
- E. Polymerase chain reaction (PCR) analysis of her cerebrospinal fluid

Answer: E The “gold standard” for diagnosing herpes simplex encephalitis is PCR analysis of cerebrospinal fluid for detection of HSV DNA. Serology is of no value in making this diagnosis acutely. A neck biopsy is reserved for patients suspected of having rabies. An electroencephalogram might show spike and slow wave activity characteristic of HSV infection, but the sensitivity and specificity are low.

1. Which of the following people is at lowest risk for severe zoster and would not necessarily need to receive antiviral medication?

- A. A 40-year-old woman with zoster involving the eye
- B. A 65-year-old man with no underlying disease
- C. A 30-year-old woman being treated for Hodgkin lymphoma
- D. A 40-year-old woman with severe pain associated with the rash
- E. A 45-year-old man with no other underlying disease

Answer: E The 45-year-old man is at least risk for complications associated with zoster. Antiviral therapy can reduce the risk for disseminated disease in immunocompromised persons and also reduce organ disease, including the eye. Antiviral therapy can reduce the acute pain associated with zoster. Persons older than 50 years are more likely to have complications associated with zoster and should be treated with antiviral therapy. (Recommendations for antiviral therapy are reported in Cohen JL. Herpes zoster. *N Engl J Med*. 2013;369:1766-1767.)

2. Which of the following persons should receive the zoster vaccine?

- A. An 80-year-old woman
- B. A 65-year-old man with Hodgkin disease
- C. A 45-year-old man
- D. A 66-year-old woman receiving 25 mg of prednisone daily for lupus
- E. A 60-year-old man with HIV and a CD4 cell count <200/ μ L

Answer: A Vaccine is approved by the Advisory Committee on Immunization Practices for persons older than 60 years. The vaccine is contraindicated in persons with hematologic malignancies and patients receiving 20 mg or more of prednisone daily. It is not approved by the U.S. Food and Drug Administration for persons younger than 50 years. The vaccine is contraindicated in persons with CD4 cell counts of $\leq 200/\mu$ L. (Recommendations for the zoster vaccine are reported in Harpaz R, Ortega-Sanchez IR, Seward JF, et al. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR Recomm Rep*. 2008;57:1-30.)

3. A 30-year-old man who received a hematopoietic stem cell transplant 2 months ago has a disseminated vesicular rash. He had stopped taking his valacyclovir prophylaxis. Which is the most sensitive and specific test to determine whether his rash is due to varicella-zoster virus (VZV)?

- A. Direct fluorescent antibody staining of cells from a skin lesion
- B. Culture of a skin lesion for VZV
- C. Polymerase chain reaction testing of a skin lesion for VZV
- D. Tzanck smear (cytology) of a skin lesion
- E. Antibody test for VZV

Answer: C The patient's rash could be due to herpes simplex or enterovirus. Polymerase chain reaction is the most sensitive and specific test for VZV. The direct fluorescent antibody test is very specific but requires sufficient numbers of cells and lesions and therefore is less sensitive. VZV is very labile, and cultures are often negative, especially if not received in the laboratory rapidly. The Tzanck smear does not distinguish HSV from VZV. Antibody testing is not useful to make a diagnosis of the cause of the rash. (Comparison of the VZV polymerase chain reaction test with other tests is reported in Sauerbrei A, Eichhorn U, Schacke M, et al. Laboratory diagnosis of herpes zoster. *J Clin Virol*. 1999;14:31-36.)

1. Which of the following is the best diagnostic test to document clinically important cytomegalovirus (CMV) infection?

- A. Tissue culture of blood
- B. Tissue culture of urine
- C. Cytology of urine
- D. CMV-specific immunoglobulin M (IgM) antibody in blood
- E. Quantitative polymerase chain reaction (PCR) for CMV DNA

Answer: E Tissue culture of blood is very insensitive compared with either antigenemia or DNAemia. Urine may remain positive by any assay for months to years after primary infection and is therefore not a specific marker of clinically important CMV disease. Cytology of urine is an insensitive assay. IgM antibody may be undetectable during infections associated with CMV reactivation or may be detectable in the absence of CMV disease. CMV PCR is a sensitive assay for CMV viremia, which usually is positive in clinically significant CMV infection of any organ.

2. CMV retinitis is best diagnosed by which of the following?

- A. PCR of vitreous fluid
- B. Tissue culture of blood
- C. Ophthalmologic examination
- D. Retinal biopsy
- E. CMV PCR on blood

Answer: C PCR of vitreous fluid or retinal biopsy requires a specimen obtained by a highly skilled operator and is not readily available. Tissue culture of blood is an insensitive assay for active CMV infection. CMV PCR on blood is a sensitive assay for CMV viremia but does not identify specific end organ disease.

3. Which is the best choice for treating systemic CMV infection?

- A. Oral valganciclovir
- B. Cidofovir
- C. Foscarnet
- D. Intravenous valganciclovir
- E. Oral ganciclovir

Answer: A Cidofovir and foscarnet are more toxic than valganciclovir and are thus not first-line therapy. Valganciclovir is not available in an intravenous form, and oral ganciclovir has been supplanted by oral valganciclovir and is no longer commercially available in many countries.

4. Which of the following is true?

- A. Nearly 90% of U.S. adults are infected with CMV by age 25 years.
- B. Primary CMV infection is usually asymptomatic.
- C. Aerosols are the primary route of CMV spread in the population.
- D. All CMV-seronegative patients should receive blood transfusions only from CMV-seronegative donors.
- E. Retinitis is the most frequent manifestation of CMV infection in transplant recipients.

Answer: B Approximately 50% of U.S. adults are CMV-seropositive by age 35 years. The primary means of spread is by direct contact with bodily secretions. CMV-seronegative blood is preferable for immunocompromised or pregnant seronegative recipients. In developed countries, little, if any, CMV is transmitted by blood transfusion. Retinitis is a rare manifestation of CMV disease in transplant recipients, in marked contrast to untreated patients with AIDS.

5. Which of the following is true for stem cell transplant (SCT) recipients?

- A. Only CMV-seronegative recipients need to be monitored for CMV viremia.
- B. Valganciclovir is the best prophylactic medication.
- C. Hyperimmune CMV immunoglobulin should be given to all recipients before transplantation.
- D. Three months of therapy with valganciclovir prevents 95% of late-onset CMV disease.
- E. None of the above

Answer: E All SCT recipients need to be monitored for the development of CMV viremia, irrespective of CMV serostatus. CMV disease occurs more commonly by reactivation of latent virus in a seropositive patient than primary infection from a seropositive donor to a seronegative recipient. Valganciclovir prophylaxis for SCT recipients should be used only if the patient cannot be monitored for the development of CMV viremia. Many SCT patients will not become viremic and would not have required prophylactic drug with the attendant toxicities, especially to bone marrow. Hyperimmune CMV immunoglobulin is very expensive and not superior to monitoring SCT patients for CMV viremia and treating when blood assays are positive. "Late-onset" CMV viremia and disease is a frequent event after valganciclovir treatment has been discontinued.

Ch / 378

RETROVIRUSES OTHER THAN HUMAN IMMUNODEFICIENCY VIRUS

1. A 35-year-old white woman from suburban Chicago arrives at your office having called for an emergency appointment because she was refused as a first-time blood donor owing to a positive virus test result. She received a blood transfusion as a child in the early 1980s and is concerned that she is positive for AIDS. When you contact the blood bank, the test result is positive for HTLV-2 (based on multiple bands on Western blot) and negative for HIV. After you explain to her the difference between HIV and HTLV, you make the following recommendations.

- A. She should be seen every 6 months for a complete blood count to monitor her for possible leukemia.
- B. She should see a neurologist annually to look for neurologic disease.
- C. If she becomes pregnant, she should avoid breast-feeding her baby.
- D. She can resume sexual activity with no restrictions.
- E. She should have a CD4 test to make sure that she does not have AIDS.

Answer: C In the United States, all blood donors are screened for HTLV in addition to other blood-borne viruses. A positive HTLV test result is often misinterpreted as HIV, and the first task of the physician is to reassure the patient about the difference between HIV and HTLV. Because the patient is infected with HTLV-2, she is not at risk for hematologic disease. For HTLV-1, the risk for leukemia is mainly in patients with early-life exposure, whereas HTLV-associated myelopathy can occur as a result of later blood transfusion with HTLV-1–infected blood. There is no need for frequent monitoring for disease among patients with either HTLV-1 or HTLV-2, although a baseline complete blood count with differential is warranted, as is careful attention to neurologic signs and symptoms during routine annual physicals. Because HTLV-1 and probably HTLV-2 can be transmitted through breast milk, breast-feeding should be avoided. Because HTLV-1 and probably HTLV-2 can be sexually transmitted, couples may consider using condoms. A CD4 test is not warranted for HTLV infection.

2. Which geographic region is not endemic with HTLV-1?

- A. United States
- B. West Africa
- C. Southern Japan
- D. Caribbean
- E. Iran

Answer: A The United States has a low prevalence and incidence of HTLV-1, and most of the cases arise from people who have migrated from endemic regions, such as the West Indies, Japan, and West Africa. In a recent serosurvey of first-time blood donors, the prevalence of HTLV-1 (5.1 per 100,000) and HTLV-2 (14.7 per 100,000) was low. The strongest risk factors for both HTLV-1 and HTLV-2 seropositivity are female sex, older age, and nonwhite race/ethnicity.

3. Which factor uniquely distinguishes HTLV-1 from HIV-1?

- A. Prolonged asymptomatic infection
- B. Sexual transmission
- C. Integration into the host genome
- D. Targets CD4+ T cells
- E. Immortalized cells

Answer: E HIV-1 and HIV-2 belong to the genus Lentivirus, whereas HTLV viruses belong to the genus Deltaretrovirus. Both deltaretroviruses and lentiviruses are associated with prolonged asymptomatic infections, both target CD4+ T cells, both integrate into the host genome, and both are transmitted sexually. However, HIV-1 and HIV-2 have cytopathic effects on T cells, whereas the HTLVs transform T cells into immortalized cell lines.

Ch / 379 ENTEROVIRUSES

1. An 18-year-old female college freshman presents to the emergency department in early autumn for evaluation of severe headache of 36 hours' duration. She has had two episodes of nonprojectile emesis and complains of diffuse myalgia, photophobia, and phonophobia. She has had no ill contacts and has never been sexually active. She received conjugated meningococcal vaccine the summer before beginning college, and her childhood immunizations are complete. She has no significant past medical history and takes no medications other than oral contraceptives. Physical examination findings: temperature, 38.5° C; heart rate, 100/minute; respiratory rate, 20/minute; blood pressure, 110/70 mm Hg. She appears mildly distressed but is awake, alert, and talkative. Her pharynx is slightly injected. Her neck is tender to flexion. Her neurologic examination reveals positive Kernig and Brudzinski signs. Funduscopy reveals normal optic discs. Which of the following is the most likely etiology of this woman's syndrome?

- A. Echovirus 9
- B. *Neisseria meningitidis* type C
- C. Human immunodeficiency virus
- D. *Haemophilus influenzae* type b
- E. None of the above

Answer: A The symptoms and mild clinical findings together with the time of year are consistent with an enteroviral infection. *Neisseria meningitidis* type C would be unlikely in this patient. She received conjugated meningococcal vaccine before starting college. Strains A, C, W-135, and Y are covered by the conjugated meningococcal vaccine. The patient has no risk factors for the acquisition of human immunodeficiency virus. The patient has received all of the childhood vaccinations, which would have included conjugated *Haemophilus influenzae* type b vaccine.

2. An 18-year-old man is brought to the emergency department for evaluation of fever of 2 days' duration and headache. The onset of the fever was sudden. Eight hours ago, he developed a headache and neck stiffness, and he has vomited three times. He complains that the light hurts his eyes. In the last 2 weeks, multiple siblings have had nonspecific febrile illnesses. His childhood immunizations are up to date, including conjugated meningococcal vaccine. Physical examination findings: temperature,

38.2° C; heart rate, 96/minute; respiratory rate, 29/minute; blood pressure, 118/78 mm Hg. He appears moderately distressed but is awake and alert. His neck is tender to flexion, and his neurologic examination reveals positive Kernig and Brudzinski signs. A lumbar puncture is performed and reveals the following: red blood cells, 0; white blood cells, 75/ μ L: 95% lymphocytes, 5% neutrophils; protein, 65 mg/dL; glucose, 90 mg/dL; Gram stain, no organisms seen. Which of the following studies would most likely establish the etiology of this adolescent's syndrome?

- A. Cell culture detection of the etiologic agent from the cerebrospinal fluid (CSF)
- B. Reverse transcription–polymerase chain reaction (RT-PCR) detection of the etiologic agent from the CSF
- C. Magnetic resonance imaging of the brain
- D. Serologic testing for the etiologic agent from the CSF
- E. All of the above

Answer: B RT-PCR is the method of choice for the detection of the enteroviruses. RT-PCR can detect even noncultivable enterovirus serotypes. It has greater sensitivity than cell culture and can be performed in hours. Cell culture has been replaced by RT-PCR as the diagnostic method. The clinical usefulness of cell culture is limited by its lack of sensitivity, the time required to obtain a positive result, and the lack of growth of some enterovirus serotypes. Neuroimaging in cases of viral meningitis is generally unrevealing. Serologic testing is of limited use because of the large number of serotypes that compose the genus Enterovirus. A four-fold change in antibody titer to a specific serotype of enterovirus in paired acute and convalescent sera is required for diagnosis. The clinical utility of serologic testing is limited by the need for acute and convalescent specimens.

3. A 31-year-old man is being evaluated for sudden onset of chest pain involving the lower ribs and sternum. The pain, which is described as stabbing and which occasionally radiates to his shoulder, is exacerbated by deep inspiration or movement. The onset of the pain was preceded by 5 days of fever, headache, malaise, and anorexia. His past medical history is noncontributory. Physical examination findings: temperature, 38.5° C; heart rate, 116/minute; respiratory rate, 32/minute; blood pressure, 128/88 mm Hg. He is in obvious pain but is awake and alert. His ears, nose, and throat are normal. His neck is supple. Heart sounds are normal. He is tachypneic and breathing shallowly, but his lungs are clear. His abdominal examination findings are normal. A chest radiograph and electrocardiogram are both normal. Which of the following is the most likely syndrome?

- A. Pneumonia due to enterovirus 68
- B. Myocarditis due to coxsackievirus B3
- C. Pleurodynia due to coxsackievirus B5
- D. Herpangina due to coxsackievirus A4
- E. None of the above

Answer: C The sudden onset of chest pain, preceded by fever and vague constitutional symptoms, is characteristic of pleurodynia. The pain may be exacerbated by deep breathing or movement. Radiation of the pain to the shoulders, back, or neck may occur. The absence of pulmonary findings (cough, wheezing) and a normal chest radiograph argue against an enteroviral pneumonia. Enteroviral myocarditis may be preceded by an upper respiratory tract infection. Common symptoms include dyspnea, chest pain, and fatigue. Physical examination may reveal a gallop rhythm or a pericardial friction rub. Cardiomegaly may be seen on the chest radiograph. Electrocardiographic findings vary and include low-voltage QRS complexes, ST segment depression, T wave inversion, pathologic Q waves, ventricular arrhythmias, and heart block. Herpangina begins abruptly with high fever; sore throat, mild cervical lymphadenopathy, sialorrhea, and dysphagia are common. An enanthem consisting of papulovesicular, grayish white lesions with an areola of erythema is seen in the mouth and throat.

4. A large community epidemic of echovirus 30 meningitis is affecting all age groups. Which of the following is the most likely mode of transmission of the virus?

- A. Respiratory
- B. Fomites
- C. Blood-borne
- D. Fecal-oral
- E. All of the above

Answer: D The majority of enteroviruses are transmitted through the fecal-oral route. A few enteroviruses responsible for upper and lower respiratory tract infection are transmitted by the respiratory route. Fomites have been associated with the transmission of enteroviruses associated with hemorrhagic conjunctivitis but are not the major mode of transmission. Blood-borne transmission of the enteroviruses has not been reported.

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ROTAVIRUSES, NOROVIRUSES, AND OTHER GASTROINTESTINAL VIRUSES

1. The principal agent of sporadic, severe gastroenteritis in young children worldwide is

- A. Rotavirus
- B. Norovirus
- C. Astrovirus
- D. All of the above
- E. None of the above

Answer: A With the advent of rotavirus vaccines, norovirus has become the leading cause of medically attended acute gastroenteritis in the United States. Worldwide, however, rotavirus continues to be the first cause of severe gastroenteritis.

2. The most probable diagnosis of an adult with viral acute gastroenteritis related to a food-borne outbreak is

- A. Rotavirus
- B. Norovirus
- C. Poliovirus
- D. All of the above
- E. None of the above

Answer: B Of these infections, only noroviruses are associated with food-borne gastroenteritis outbreaks and disease in adults.

3. Diagnosis of both norovirus and rotavirus acute gastroenteritis can optimally be performed with

- A. Viral culture
- B. Enzyme-linked immunosorbent assay (ELISA)
- C. Quantitative reverse transcription–polymerase chain reaction (RT-PCR) testing using a threshold level
- D. B or C
- E. None of the above

Answer: C Quantitative RT-PCR (using a threshold level) is an optimal diagnostic strategy for both rotavirus and norovirus. RT-PCR for rotavirus without use of a threshold level will identify viral RNA in asymptomatic children. ELISA can be used for the diagnosis of rotavirus but not norovirus because these assays have variable sensitivity, depending on the norovirus genotype.

1. Two distinct diseases caused by hantaviruses are hantavirus pulmonary syndrome and

- A. Argentine hemorrhagic fever
- B. Lassa fever
- C. Hantavirus hepatic syndrome
- D. Hemorrhagic fever with renal syndrome
- E. Adult T-cell leukemia

Answer: D The genus Hantavirus of the Bunyaviridae family is divided into Old and New World groups. The Old World hantaviruses, such as Hantaan, Seoul, and Puumala, among many others, cause hemorrhagic fevers with prominent renal involvement across Europe and Asia. New World hantaviruses, such as Sin Nombre and Andes, among many others, cause a viral hemorrhagic fever named hantavirus pulmonary syndrome, sometimes also called hantavirus cardiopulmonary syndrome to emphasize the significant cardiogenic component of this disease. A thorough travel history can help narrow the differential diagnosis, although there can be, at times, overlap between the two syndromes. One Old World hantavirus, Seoul, can be found virtually worldwide because its reservoir, the common Norway rat, has been spread globally through transport on ships.

2. The antiviral drug ribavirin is most clearly indicated for which of the following viral hemorrhagic fevers?

- A. Ebola hemorrhagic fever
- B. Yellow fever
- C. Lassa fever
- D. Omsk hemorrhagic fever
- E. Rift Valley fever

Answer: C The only currently available specific antiviral therapy for any viral hemorrhagic fever is the guanosine analogue ribavirin. The best data are for Lassa fever, in which intravenous ribavirin has been shown to decrease mortality in severe disease from 55% to 5% when it is begun within the first 6 days of illness.¹ Ribavirin efficacy has also been demonstrated for hemorrhagic fever with renal syndrome due to Hantaan virus. The drug appears to be efficacious in other arenavirus hemorrhagic fevers and Crimean-Congo hemorrhagic fever, but few randomized controlled clinical trials have been performed for these syndromes. Ribavirin is not efficacious and should not be used for Ebola or Marburg hemorrhagic fevers.

1. McCormick JB, King IJ, Webb PA, et al. Lassa fever. Effective therapy with ribavirin. *N Engl J Med*. 1986;314:20-26.

3. Viral hemorrhagic fever syndromes

- A. Can usually be easily distinguished from other common febrile diseases on clinical grounds early in the course of disease
- B. Can be confirmed only through virus culture in a high-containment laboratory
- C. Are usually characterized by copious bleeding, often leading to exsanguination and death
- D. Typically have incubation periods of days to weeks
- E. Should be routinely treated with intravenous corticosteroids

Answer: D After an incubation period ranging from days to weeks, most patients with viral hemorrhagic fever present with nonspecific signs and symptoms difficult to distinguish from a host of other febrile illnesses. Laboratory confirmation is therefore imperative and can be performed through a variety of methods, including the enzyme-linked immunosorbent assay, polymerase chain reaction, virus culture, and immunohistochemistry on postmortem tissues. Most of these assays do not involve live virus and thus can be performed outside of a high-containment laboratory, noting that the specimen to be tested may nevertheless be infectious. Despite the name, external bleeding is seen in a minority

of cases of viral hemorrhagic fever, especially early in the course of disease. Death in fatal cases is not typically due to exsanguination but rather to an intense inflammatory process akin to septic shock leading to multiorgan system failure. Adrenal or pituitary gland necrosis with consequent vascular collapse has been postulated but not specifically demonstrated. Corticosteroids are not indicated unless adrenal insufficiency is strongly suspected, the target blood pressure is not maintained despite adequate fluid repletion and vasopressors, or cerebral edema is suspected.

4. Which of the following is the most essential component of control of Lassa virus transmission between humans?

- A. Immediate isolation of all patients in the incubation period
- B. Placement of insecticide-treated bed nets and room screens in patient rooms
- C. Donning of "space suits" by health care personnel working in patient isolation wards
- D. Placement of suspected case-patients in hermetically sealed rooms
- E. Routine barrier nursing precautions (gloves, gowns, and masks)

Answer: E Human-to-human transmission of Lassa virus, as for the other directly communicable hemorrhagic fever viruses, is through direct contact with infected blood and body fluids. Routine barrier nursing precautions to prevent parenteral and droplet exposure are protective in most cases, although "viral hemorrhagic fever precautions" consisting of the use of surgical masks, face shields, double gloves, gowns, head and shoe covers, and protective aprons are implemented for added safety once the syndrome is suspected. Patients are not infectious during the incubation period. There is little evidence for aerosol transmission between humans. Hermetically sealed isolation chambers are not required, although it is prudent to place the patient in a negative airflow room if it is available. The reservoir for Lassa virus is the rodent *Mastomys natalensis*, commonly called the natal mastomys or multimammate rat. There is no arthropod vector.

5. A 23-year-old otherwise healthy woman is seen with complaints of fever, malaise, headache, and muscle aches for the past 5 days. She recently returned from a church mission trip in which she assisted physicians and nurses treating patients in a resource-poor area of Bolivia. She is in moderate distress with vital signs as follows: temperature, 102.5° F; blood pressure, 105/65 mm Hg; pulse, 120; and respiratory rate, 24. Her conjunctivae are injected, and a petechial rash is noted over her torso. Initial laboratory findings show moderate leukopenia, hemoconcentration, and mild to moderate thrombocytopenia. You suspect infection with which of the following hemorrhagic fever viruses?

- A. Machupo virus
- B. Lujo virus
- C. Ebola virus
- D. Junín virus
- E. Sin Nombre virus

Answer: A With the exception of dengue virus, hemorrhagic fever viruses are zoonotic and are maintained in nature in mammalian reservoirs. The endemic area of any given hemorrhagic fever virus is restricted by the distribution of its natural reservoir or arthropod vector. Knowledge of the geographic limits of the reservoir, along with a detailed travel history, is key to assessing the likelihood of exposure to a given hemorrhagic fever virus. In this case, the patient may have been exposed to Machupo virus, the causative agent of Bolivian hemorrhagic fever, which is endemic only in Bolivia. Junín virus is also found in South America but is restricted to the Argentine pampas. Ebola and Lujo viruses are endemic in Africa. Sin Nombre virus, which is one of the causative agents of hantavirus pulmonary syndrome, is found in North America. Other hantaviruses are found in Bolivia, but the patient's presentation and laboratory results are not consistent with hantavirus pulmonary syndrome, in which rash would be unusual and leukocytosis with immunoblasts is classically noted. The fact that she had potential exposure to human blood or body fluids while assisting physicians and nurses should heighten suspicion of a viral hemorrhagic fever.

1. A 24-year-old woman presents with 3 weeks of arthralgia involving the fingers and toes. The illness began suddenly with fever and headache 2 weeks ago, about 1 week after returning from her 2-year tour in the Peace Corps in Peru teaching English to children of Amazon lumber workers. Fever and headache resolved after the first week of illness. During the second week of illness, she noticed a blotchy red rash on her torso and arms. She denies joint swelling. Examination was unremarkable. Laboratory testing excluded parvovirus B19, rubella, Epstein-Barr virus, hepatitis B virus, hepatitis C virus, and coxsackievirus infections. The most likely diagnosis is

- A. Chikungunya virus infection
- B. Dengue virus infection
- C. Mayaro virus infection
- D. Ross River virus infection
- E. Sindbis virus infection

Answer: C The geographic exposure would eliminate chikungunya virus, Ross River virus, and Sindbis virus as causative agents. Mayaro virus and dengue have overlap in their geographic distribution. The history suggests a milder course with mild arthralgias, which would argue against dengue, also called breakbone fever. At this juncture, the diagnosis can be confirmed by finding a positive Mayaro virus-specific serum IgM.

2. A 67-year-old retired businessman from Greenwich, Connecticut, with a known history of insulin-dependent type 2 diabetes mellitus and chronic sinusitis was in fair health until August, when he had onset of fever, headache, nausea, and myalgia. He noticed a nonpruritic macular rash over his torso soon after the fever began; 4 days later, the involved skin began peeling. His headache then began to worsen. During the second week of illness, he developed nuchal rigidity and became obtunded, at which time he was hospitalized. A social history revealed a pigeon fancier hobby. Examination revealed somnolence with difficult arousal, nuchal rigidity, and flaccid paralysis. A differential diagnosis of West Nile virus infection was entertained. At this juncture, the best way to demonstrate that the neurologic presentation is due to West Nile virus infection is

- A. Detect West Nile virus in peripheral blood by reverse transcription– polymerase chain reaction (RT-PCR)–based detection of viral RNA
- B. Detect West Nile virus IgM antibody in serum
- C. Detect West Nile virus IgM and IgG antibody in serum
- D. Save a serum sample at this time and demonstrate a four-fold increase in West Nile virus IgG in a convalescent serum sample obtained 3 weeks later
- E. Detect West Nile virus IgM antibody in cerebrospinal fluid

Answer: E At this time, during the second week of illness, detection of viremia is unlikely. Demonstrating West Nile virus IgM in the serum confirms a recent West Nile virus infection but does not definitively demonstrate that the neurologic involvement is caused by West Nile virus in this elderly man with diabetes and chronic sinusitis. Note that the IgM may persist for up to 1 year in a minority of patients; subclinical infection may have occurred more remotely in this man. Detecting a four-fold increase in West Nile virus IgG in convalescent serum confirms a recent infection but does not definitively demonstrate that the neurologic involvement is due to West Nile virus. IgM normally does not cross the blood-brain barrier, so detecting West Nile virus IgM in the cerebrospinal fluid demonstrates central nervous system infection with the virus, although leakiness in the blood-brain barrier from another cause with passive movement of serum IgM into the cerebrospinal fluid cannot be completely excluded.

3. A 20-year-old male premedical student from Chicago enjoyed his spring break rock climbing in the Rocky Mountains with his girlfriend. One week later, during his organic chemistry midterm, he developed headache and myalgia. He attributed his symptoms to the previous all-nighter studying for his examination. That evening he developed photophobia, eye pain, and weakness. The following morning, he noticed punctate red dots, which did not blanch on pressure, over his torso. In the Student Health Service, palatal petechiae, petechial rash on the torso, generalized lymphadenopathy, and mild splenomegaly were noted. Laboratory testing showed mild leukopenia and thrombocytopenia. A presumptive diagnosis of Rocky Mountain spotted fever was made by the Health Service Director, and the patient was started on doxycycline. However, you begin to doubt the diagnosis the following day when the patient fails to develop the classic spotted fever rash (see Chapter 327). Diagnostic tests are pending. The likely diagnosis is

- A. Colorado tick fever
- B. Dengue
- C. Disseminated gonorrhea
- D. Rocky Mountain spotted fever
- E. None of the above

Answer: A The exposure and course are consistent with Colorado tick fever. Dengue is unlikely because the Rockies are outside of the geographic distribution for dengue, which is found in the southeast United States and other tropical and subtropical climates. Patients with disseminated gonorrhea present with an arthritis-dermatitis syndrome, in which generalized arthralgias and myalgias quickly settle into one or more locations with inflammatory arthritis or tenosynovitis; scattered 1- to 3-mm pustules may evolve necrotic centers. This patient lacked inflammatory arthritis or tenosynovitis; his exanthem consisted of multiple petechiae rather than pustules, and the lesions were more plentiful than the pustules typically seen in disseminated gonorrhea. The rash argues against Rocky Mountain spotted fever, in which the “spotted” rash of 1- to 5-mm macules classically becomes purpuric. The patient had petechiae that did not blanch on pressure. However, the Health Service Director was not incorrect in starting doxycycline. The classic rash can appear later or not at all in the course of Rocky Mountain spotted fever, and serologic diagnosis often requires acute and convalescent sera. Doxycycline can be life-saving when it is started early in suspected Rocky Mountain spotted fever.

4. An 18-year-old U.S. Marine stationed in Helmand Province, Afghanistan, flew home on emergency leave to see her sick father in Ottumwa, Iowa. Four days after arriving, she developed headache, stiff neck, eye pain, photophobia, arthralgia, and chest pain. Examination showed a macular rash measuring 2 × 4 cm with scattered papules within it on her left calf. Laboratory testing showed leukopenia and lymphopenia. Cerebrospinal fluid showed mild pleocytosis. The likely diagnosis is

- A. Chikungunya fever
- B. Dengue
- C. O’nyong-nyong fever
- D. Phlebotomus fever
- E. Ross River fever

Answer: D In Afghanistan, the potential for exposure to the sandfly vector is significant. These small flies may pass through mosquito netting. Among British soldiers in Helmand Province, 52% of undifferentiated fever cases were attributed to phlebotomus fever. Myalgias may be sufficiently severe to be perceived as pleurodynia. Mild aseptic meningitis is common. Chikungunya fever is endemic in sub-Saharan Africa, India, the Philippines, and Southeast Asia and has spread to islands in the Indian Ocean and the Caribbean, but it is not found in the mountains of Afghanistan. Likewise, dengue is distributed in tropical and subtropical climates. Recent outbreaks of o’nyong-nyong fever have occurred in Uganda but not in Afghanistan. Ross River virus is limited to east of Weber’s line, the virtual line that separates the Australian biogeographic zone from the Asian biogeographic zone. Furthermore, the rash in Ross River virus infection is a more widely distributed maculopapular rash with occasional vesicles, papules, or petechiae over the torso, extremities, face, palms, and soles; the

rash also may desquamate. The rash described in this patient is more localized and is attributable to the sandfly bites.

5. A 26-year-old hipster born and living in Manhattan spends winters in Jamaica with friends. Shortly after returning to New York this year, she experienced sudden-onset fever, severe headache, eye pain, nausea, vomiting, myalgia, and arthralgia. By the next day, the joint and muscle pain became severe. Two days later, she sought medical attention. Examination showed an ill-appearing woman, alert but in apparent pain. Temperature was 100.5° F, pulse 104/minute, blood pressure 92/50 mm Hg, and respirations 28/minute. Multiple petechiae appeared on her left arm distal to where the blood pressure cuff was applied. Cervical and inguinal lymph nodes were palpable and nontender. Joint examination was unremarkable. Laboratory testing showed white cell count of 1500/ μ L and platelet count of 55,000/ μ L. Hemoglobin was 19 g/dL. Prothrombin time was 22 seconds. The pregnancy test was positive. A diagnosis of dengue virus infection was suspected. Dengue virus serology was positive for IgG antibody to serotype 1 as well as for IgM and IgG antibodies to serotype 2. The diagnosis is

- A. Dengue virus infection, classic
- B. Dengue virus infection, hemorrhagic fever
- C. Dengue virus infection, shock syndrome
- D. Dengue virus infection, classic with preeclampsia

Answer: B The patient began with classic dengue features but developed low-normal blood pressure, tachycardia, and hemoconcentration suggestive of volume loss. The positive tourniquet sign with the development of petechiae distal to the blood pressure cuff is a warning sign that hemorrhagic fever has developed. The presence of thrombocytopenia and prolonged prothrombin time provide laboratory support. The serologic evidence of a previous dengue virus infection with serotype 1 (IgM–, IgG+) supports the increased risk for development of hemorrhagic fever due to enhancement of immune response by preexisting antiviral antibodies. The patient has not yet developed hemorrhagic shock syndrome, but prompt intervention with supportive measures should improve prognosis. The patient is pregnant, which may worsen the clinical picture, but her low blood pressure argues against preeclampsia.

**EPIDEMIOLOGY AND DIAGNOSIS OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION
AND ACQUIRED IMMUNODEFICIENCY SYNDROME**

1. Which of the following statements is *incorrect*:

- A. In 2013, 2.1 million people became newly infected, half of whom were young individuals between the age of 15 and 24 years.
- B. By the end of 2013, 35 million people were living with HIV globally.
- C. The epidemic has stabilized in many regions, with new infections decreasing by 50% or more in 25 countries.
- D. HIV prevalence and incidence had declined sharply in 2013 in Eastern Europe and Central Asia.

Answer: D Prevalence and incidence have increased sharply over the past decade in Eastern Europe and Central Asia, partially driven by injection drug use and sexual transmission. In addition, treatment for those infected has also lagged behind in these regions.

2. Which of the following regions has yet to attain over 50% coverage of antiretroviral therapy for eligible individuals?

- A. Latin America
- B. The Caribbean
- C. Oceania
- D. Eastern Europe and Central Asia
- E. Eastern and southern Africa

Answer: D Eastern Europe and Central Asia have reached coverage of only 25% of antiretroviral therapy for HIV-infected individuals eligible for treatment. The Middle East and North Africa have attained only a 15% coverage rate, whereas Latin America, the Caribbean, Oceania, and Eastern and southern Africa have all attained coverage rates over 56 to 69%.

3. Which of the following statements regarding the HIV epidemic in the United States is *false*?

- A. The incidence of new HIV infections in 2012 has remained relatively stable over the past decade at approximately 50,000 new cases.
- B. The incidence of HIV infection has declined in men who have sex with men (MSM), but has increased among injecting drug users.
- C. HIV occurs at disproportionately higher rates among African Americans and Hispanics compared to white and other ethnicity groups.
- D. Most women acquire HIV through unprotected heterosexual exposure.

Answer: B The frequency of new HIV infections among MSM continues to be relatively stable or in some areas slightly increased. There have been no observations within the last decade of any significant declines in HIV among this population. In contrast, HIV incidence has decreased among injection drug users.

4. The U.S. Preventive Services Task Force recently recommended that clinicians should screen for HIV in all adolescents and adults aged 15 to 65 years of age. This recommendation was based on which of the following facts?

- A. There is increasing evidence of clinical benefit through early antiretroviral therapy for HIV-infected persons.
- B. A recent randomized, clinical trial demonstrated that antiretroviral therapy is effective in reducing HIV transmission.
- C. Approximately 20% of HIV-infected individuals have never been tested and are unaware of their infection.
- D. Use of antiretroviral therapy during pregnancy has been shown to be effective in decreasing mother-to-child transmission of HIV.
- E. All of the above.

Answer: E All of the above supporting statements for early diagnosis and treatment providing benefit to HIV infected persons provided the evidence for the USPSTF recommendations for routine screening for HIV.

1. What is the most likely cause of CD4 depletion in HIV-infected patients?

- A. Chronic immune activation
- B. Direct killing of productively infected cells
- C. Infection by opportunistic pathogens
- D. Metabolic disturbances

Answer: A Chronic immune activation is thought to play the most significant role, although a recent study suggests that non-productively infected cells may die from a protective host response. Only 1% of cells are productively infected, and therefore it is felt that the death of these cells cannot explain the level of CD4 depletion seen.

2. At what CD4 count do patients become susceptible to *Pneumocystis jiroveci*?

- A. 50 cells/ μ L
- B. 100 cells/ μ L
- C. 200 cells/ μ L
- D. 500 cells/ μ L

Answer: C Clinical studies have shown that patients become susceptible to *Pneumocystis jiroveci* at a CD4 count of less than 200 cells/ μ L. *Cryptococcus neoformans* and *Toxoplasma gondii* infections occur at CD4 counts < 100 cells/ μ L; and *Mycobacterium avium* complex and CMV infections occur at CD4 counts < 50 cells/ μ L.

3. HIV-1–infected patients are highly susceptible to invasive pneumococcal disease because of:

- A. Immune activation.
- B. Dysfunction of B cells.
- C. Apoptosis of CD8+ T cells.
- D. Increased exposure to pneumococcus.
- E. Hyposplenism.

Answer: B Although HIV-1 infection typically causes a defect of cellular immunity, humoral immunity is also affected because of a B-cell dysfunction and patients become susceptible to bacterial infections.

4. At what point after HIV infection do patients develop the acute retroviral syndrome?

- A. 2 weeks
- B. 6 weeks
- C. 3 days
- D. 3 months

Answer: A Patients typically develop the constellation of symptoms known as the acute retroviral syndrome 2 weeks after infection. At that point, as a result of the massive early infection, plasma levels of virion-associated HIV-1 RNA of more than 1 million copies/mL are typically seen in plasma.

5. What is the mechanism of the drop in HIV-1 RNA to the set point level in primary infection?

- A. The development of an HIV-1–specific CD4+ T-cell immune response
- B. The establishment of the latent reservoir
- C. The development of neutralizing antibodies
- D. The development of an HIV-1–specific CD8+ T-cell immune response

Answer: D The development of the HIV-specific CD8+ T-cell response has been associated with partial control of viral replication in clinical studies and depletion of CD8+ T cells in an animal model abrogates this control of viremia.

6. Which of the following is the biggest barrier to the eradication of HIV-1?

- A. The establishment of the latent reservoir
- B. Chronic immune activation
- C. B-cell dysfunction
- D. Microbial translocation

Answer: A The quiescent memory CD4+ T cells of the latent reservoir probably do not express HIV antigens and thus are not targeted by the immune response. They are also not effectively targeted by antiretroviral therapy, thus preventing the eradication of HIV-1.

1. Which of the following animals represents the *most likely* source of HIV-1?

- A. Sooty mangabey
- B. Chimpanzee
- C. Gorilla
- D. Macaques
- E. Mandrill

Answer: B HIV-1 is responsible for over 30 million infections worldwide and is closely related to a simian immunodeficiency virus (SIV) present in chimpanzee populations. Although gorillas have an SIV, that virus is more distantly related to HIV-1 than the chimpanzee virus. Sooty mangabeys have SIV that is very closely related to HIV-2 but not to HIV-1. Macaques and mandrills are species of monkeys with SIV variants that are only distantly related to HIV.

2. Which of the following inhibits HIV infection by introducing numerous G-to-A mutations in the HIV genome?

- A. Tetherin
- B. APOBEC
- C. TRIM5-alpha
- D. Vif

Answer: B APOBEC is a cytidine deaminase and one part of the innate immune system that inactivates virus by introducing multiple G-to-A changes, which result in multiple mutations and stop codons. Tetherin is a cell surface protein that retains virions at the cell surface and is antagonized by VPU. TRIM5-alpha is involved in blocking uncoating before reverse transcription, and Vif is a viral protein that abrogates Apobec activity by excluding it from incorporation into the virion.

3. HIV-2 is naturally resistant to which of the following agents?

- A. Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- B. Nucleoside reverse transcriptase inhibitors (NRTI)
- C. Protease inhibitors (PI)
- D. Integrase inhibitors (INSTI)

Answer: A HIV-2 is only distantly related to HIV-1 and encodes a reverse transcriptase that is naturally resistant to non-nucleoside reverse transcriptase inhibitors. HIV-2 remains susceptible to NRTI, PI, and integrase inhibitors. It is critical that individuals with HIV-2 or HIV-1/2 *not* be treated with NNRTI, because mutants resistant to the other components of the regimen will emerge.

4. HIV virion assembly takes place:

- A. At the plasma membrane.
- B. Within the cytoplasm.
- C. At the nuclear membrane
- D. Within the nucleus.

Answer: A HIV assembles at the plasma membrane; no virus-like particles are seen in the cytoplasm or at or within the nucleus.

5. HIV protease inhibitors inhibit which of the following steps in HIV replication?

- A. Proteolytic processing of HIV Gag and Gag/pol precursors
- B. Proteolytic processing of Env precursor
- C. Proteolytic processing of the HIV core during virion uncoating
- D. Proteolytic processing of the intasome before integration

Answer: A Protease inhibitors are a key component of combination antiretroviral therapy. They block a late step in virus replication after virions have assembled. The immature virus is not infectious until after protease acts on Gag and Gag/Pol.

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PREVENTION OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

1. After occupational exposure by a health care worker to HIV through a needlestick injury, management should include which of the following?

- A. The HIV status of the exposure source patient should be determined.
- B. Postexposure prophylaxis should contain no more than two antiretrovirals.
- C. Antiretroviral therapy should be started within 72 hours of exposure and continued for 4 weeks
- D. All of the above are correct.
- E. Only a and c are correct.

Answer: E In managing health care personnel who experience occupational exposure to blood and/or body fluids that might contain HIV, the USPHS guidelines published in 2013 recommend that after occupational exposure to HIV occurs the HIV status of the exposure source be determined (if possible). Postexposure prophylaxis should be started as soon as possible (within 72 hours) and continued for 4 weeks and three or more antiretrovirals should be prescribed.

2. The most effective strategy for the prevention of sexual transmission of HIV from an infected to an uninfected partner is:

- A. Voluntary HIV counseling and testing.
- B. Antiretroviral therapy of the infected partner.
- C. Antiretroviral therapy of the uninfected partner.
- D. Prompt treatment of sexually transmitted infections.
- E. Avoidance of oral sex.

Answer: B Antiretroviral therapy to bring HIV replication below the limits of detection has proved to be an effective strategy to decrease by 96% the risk for HIV transmission among serodiscordant couples.

3. Confidential donor exclusion, HIV antibody screening, testing for antibodies to HIV-2 and p24 antigen, and nucleic acid testing has reduced the risk for HIV infection through the transfusion of blood or blood products to:

- A. Approximately 1 in 20,000.
- B. Approximately 1 in 200,000.
- C. Approximately 1 in 2,000,000.
- D. Approximately 1 in 20,000,000.

Answer: C HIV has been transmitted through the transfusion of single-donor blood and blood products, including whole blood, fresh-frozen plasma, packed red blood cells, cryoprecipitate, clotting factors, and platelets. Confidential donor exclusion, as well as the institution of HIV antibody screening in 1985, followed by additional testing for antibodies to HIV-2 and p24 antigen in 1996 and nucleic acid testing in 2002, has reduced the risk for HIV infection through the transfusion of blood or blood products to approximately 1 in 2,135,000.

4. The effectiveness of condoms in preventing heterosexual transmission of HIV has been estimated to be:

- A. As low as 60% and as high as 96% (~87%).
- B. Higher for anal than for vaginal sex.
- C. Equal for latex and natural skin condoms.
- D. Enhanced by petroleum-based lubricants.

Answer: A The effectiveness of condoms in preventing heterosexual transmission of HIV has been estimated to be 87%, but it may be as low as 60% or as high as 96%. Consistent use of latex condoms has been shown to be effective in preventing of HIV transmission at both individual and population levels. The condom should be made of latex and must be used properly. Natural skin condoms should not be used because they do not prevent transmission of HIV. Petroleum-based lubricants enhance the likelihood of rupture of latex condoms and should be avoided. If needed, water-based lubricants such as K-Y jelly should be used.

5. HIV transmission risk is highest in:

- A. Patients taking antiretrovirals.
- B. Patients with a sexually transmitted infection such as genital wart.
- C. Early HIV infection and advanced infection.
- D. An episode of a concomitant viral infection such as influenza.

Answer: C The risk for HIV transmission is highest in early HIV infection and in advanced infection, demonstrating that the HIV viral concentration in the genital secretions is the strongest predictor of the risk for transmission.

ANTIRETROVIRAL THERAPY OF HUMAN IMMUNODEFICIENCY VIRUS AND ACQUIRED IMMUNODEFICIENCY SYNDROME

1. Which CD4 cell count should prompt starting antiretroviral therapy in an HIV-infected individual?

- A. <200/ μ L.
- B. <350/ μ L.
- C. <500/ μ L.
- D. Treatment should be started regardless of CD4 cell count.

Answer: D.

2. Which treatment strategy is *not* recommended for first-line antiretroviral therapy?

- A. Two nucleoside analogue reverse transcriptase inhibitors (NRTIs) + a non-nucleoside reverse transcriptase inhibitor (NNRTI)
- B. Three NRTIs
- C. Two NRTIs + a protease inhibitor (PI)
- D. Two NRTIs + an integrase strand transfer inhibitor (INSTI)

Answer: B.

3. When should you change an antiretroviral regimen for treatment failure?

- A. HIV RNA repeatedly 50 to 200 copies/mL
- B. HIV RNA repeatedly over 500 copies/mL
- C. Any confirmed HIV RNA above the limit of detection
- D. CD4 cell count < 200 cells/ μ L

Answer: B.

4. What is the best regimen to treat both HIV and HBV infections?

- A. zidovudine/lamivudine + darunavir/ritonavir
- B. abacavir/lamivudine + raltegravir
- C. tenofovir/emtricitabine + zidovudine
- D. tenofovir/emtricitabine/efavirenz

Answer: D.

5. HIV pre-exposure prophylaxis (PrEP) should be offered to all *except*:

- A. An active heroin user.
- B. An HIV-negative partner of an HIV-positive individual with an HIV RNA of 250,000 copies/mL.
- C. A heterosexual woman with several sexual partners who “doesn’t always use condoms.”
- D. A gay man in a monogamous relationship with an HIV-negative partner.

Answer: D.

1. Which of the following opportunistic infections is most typical of HIV infection with a CD4 count less than 50 cells/mm³?

- A. Mucormycosis
- B. BK virus nephropathy
- C. Nocardiosis
- D. *Mycobacterium avium* complex disease
- E. *Listeria monocytogenes* meningitis

Answer: D Patients with HIV infection and low CD4 counts (<50 cells/mm³) characteristically develop pneumocystosis, toxoplasmosis, CMV retinitis, tuberculosis, cryptococcal meningitis, cryptosporidiosis, and disseminated *Mycobacterium avium* complex infection. Mucormycosis is typically seen in patients with neutropenia or diabetes mellitus and is rare in patients immunosuppressed because of HIV infection. *Listeria*, surprisingly, does not appear to occur with enhanced frequency among patients with HIV infection although it is an intracellular pathogen. Nocardiosis can occur in patients with HIV infection, but is unusual. BK virus causes disease in transplant recipients, with nephropathy seen in renal transplant patients. BK virus is most unusual in patients with HIV infection.

2. Which of the following peripheral blood assays is the best indicator of susceptibility to opportunistic infections for patients with HIV infection?

- A. CD4 lymphocyte count
- B. CD8 lymphocyte count
- C. Total lymphocyte count
- D. Total neutrophil count
- E. Total leukocyte count

Answer: A For HIV-infected patients, CD4 T cell counts in the peripheral blood are excellent indicators of susceptibility to opportunistic infections. There is a tight correlation between the counts and susceptibility to AIDS-defining illnesses. Counts under 200 cells/mm³ are a good estimate of susceptibility to pathogens such as *Pneumocystis pneumonia*. Counts under 100 cells/mm³ are indicators of susceptibility to CMV, *Toxoplasma*, and *Mycobacterium avium*. The total lymphocyte count also can be used, but is not nearly so specific and sensitive. CD8 suppressor cells are related to immune response, but also are not tightly correlated with infectious susceptibility. Patients with HIV infection become neutropenic only with very-late-stage disease, when their marrow is involved by certain infections or tumors, or if they have marrow suppression resulting from a drug effect or a nutritional deficiency. Neutropenia in this population is not as ominous as in patients who have had chemotherapy and who have eroded mucosal barriers.

3. For HIV-infected patients on long-term antiretroviral therapy, and viral loads less than 50 copies and CD4 counts greater than 300 cells/mm³, which of the following groups of problems are the major cause of HIV-related morbidity and mortality?

- A. *Candida*, herpes zoster, and herpes simplex
- B. Kaposi's sarcoma and multicentric Castleman's disease
- C. Progressive multifocal leukoencephalopathy and central nervous system lymphoma
- D. Accelerated liver, heart, and kidney disease
- E. Sepsis and septic shock

Answer: D For patients with HIV infection well controlled on antiretroviral therapy, accelerated liver disease, coronary atherosclerosis, renal disease, and neurocognitive disorders are emerging as major causes of morbidity. At CD4 counts greater than 300, Kaposi's sarcoma occurs, but it is not common in the United States. Similarly, at such counts progressive multifocal leukoencephalopathy and CNS

lymphoma are uncommon. Septic shock does not occur with substantially increased frequency in patients with HIV infection. They are susceptible at all CD4 counts to increased incidence of pneumococcal disease, but most cases of sepsis in this population come from predictable sources such as intravenous catheters or intravenous drug abuse.

4. For a patient with HIV infection whose CD4 count is 50 cells/mm³ and who is going to start antiretroviral therapy in the next few weeks, which of the following prophylactic drugs would be most beneficial pending sustained HIV viral suppression?

A. Fluconazole
 B. Valganciclovir
 C. Valacyclovir
 D. Trimethoprim-sulfamethoxazole
 E. Caspofungin

Answer: D Patients with CD4 counts below 200 cells/mm³ are susceptible to *Pneumocystis pneumonia* (PCP), and the susceptibility increases as the CD4 count decreases. In the pre-antiretroviral era, 70 to 80% of HIV-infected patients ultimately developed PCP if they did not take anti-pneumocystis prophylaxis. Azithromycin to prevent disseminated *Mycobacterium avium* complex infection would also be appropriate, although this option was not offered as an answer. Antiviral prophylaxis with valacyclovir would reduce the frequency of herpes simplex and herpes zoster, but this prophylaxis is not recommended in preference to treating episodes caused by these pathogens when they occur. Similarly, fluconazole could be used to reduce the likelihood of mucosal candidiasis, but the recommendation is not to give prophylaxis but to treat episodes when they occur. Caspofungin, a parental antifungal, would have no role for prophylaxis. Some drugs that are effective for prophylaxis, such as fluconazole and acyclovir, are not recommended for routine use because of potential drug interactions, drug toxicities, cost, and the fact that episodes of the targeted diseases are usually not life-threatening and can be treated when they occur acutely.

5. Which of the following vaccines would be appropriate to give to a patient with newly diagnosed HIV infection (CD4 count = 100 cells/mm³, viral load = 1 million copies) who had childhood immunizations but none since then and who will be starting on antiretroviral therapy plus chemoprophylaxis with trimethoprim-sulfamethoxazole and azithromycin in 1 week?

A. Herpes zoster vaccine
 B. Herpes simplex vaccine
 C. Pneumococcal vaccine (conjugated)
 D. Attenuated influenza vaccine
 E. Measles-mumps-rubella vaccine

Answer: C For patients with low CD 4 counts (<200 cells/mm³) it is not prudent to administer live virus vaccines such as the zoster vaccine or measles-mumps-rubella or the live attenuated influenza virus vaccine. There is no licensed vaccine for herpes simplex. Pneumococcal vaccine is important to administer. CDC guidelines and guidelines at <http://www.aidsinfo.nih.gov> provide information on the vaccine products to use. Pneumococcal vaccines are effective in reducing the morbidity of pneumococcal disease in this patient population. It may be wise to readminister this when the CD4 count has risen substantially if the initial immunization was administered when the CD4 count was below the 100 to 200 range.

1. A 47-year-old man with poorly controlled HIV infection complains of pain on swallowing both liquids and solids. His HIV viral load is 157,468 copies/mL and his CD4 count is 152 cells/mm³. He admits to poor adherence to antiretroviral therapy. On exam, he is wasted. There are white patches on his buccal mucosa. His abdominal exam is unremarkable. You recommend:

- A. Upper gastrointestinal (GI) endoscopy with biopsies and brushings of the esophagus
- B. Empirical treatment with fluconazole
- C. Ophthalmic exam for cytomegalovirus (CMV) involvement of the retina
- D. Empirical treatment with ganciclovir
- E. Oral corticosteroids for idiopathic HIV related esophageal ulcers

Answer: B The most likely diagnosis is *Candida* esophagitis causing odynophagia. Esophageal infections do not cause obstruction, so there is no dysphagia, but the esophageal contractions with swallowing cause pain in an inflamed esophagus with either liquids or solids. Oral thrush and dysphagia are 90% predictive of esophageal candidiasis. An empirical trial of an antifungal medication directed at *Candida* is an appropriate treatment, reserving upper GI endoscopy for patients who do not quickly respond to treatment. CMV, herpes, and idiopathic ulcerations of the esophagus generally occur in patients with CD4 counts below 50 cells/mm³. GI endoscopy with biopsies of the ulcers is the best way to make these diagnoses.

2. On initial laboratory reports, a 55-year-old man living with HIV/AIDS who is new to the clinic is found to have the following biochemical tests of liver function. He feels generally well. He is on a stable antiretroviral regimen with good control of HIV infection. He takes a multivitamin and Percocet for knee pain. His abdominal exam shows no hepatosplenomegaly. His CD4 count is 410 cells/mm³, and his HIV viral load is undetectable.

The most appropriate next step would be:

- A. A liver biopsy to determine whether he has cirrhosis
- B. Stop all medications and see if the biochemical tests return to normal.
- C. Test for autoimmune hepatitis with a panel including antinuclear antibody and serum protein electrophoresis.
- D. Weight reduction diet and exercise for fatty liver
- E. Test for hepatitis B and C with hepatitis B surface antigen and anti-hepatitis C antibody.

Answer: E Biochemical tests of liver function are frequently abnormal in HIV/AIDS, with mild to moderate abnormalities in the aminotransferases (AST, ALT) being the most frequent abnormalities seen. The differential diagnosis includes drug-related hepatotoxicity, fatty liver, alcohol, and overuse of acetaminophen, but autoimmune hepatitis is uncommon in a male with HIV/AIDS. Over 25% of persons with HIV infection are coinfecting with hepatitis C or hepatitis B virus. Chronic hepatitis B can be diagnosed by a positive hepatitis B surface antigen (which is also seen transiently in acute infection). Chronic hepatitis C infection is diagnosed by a positive anti-hepatitis C antibody (anti-HCV), and chronic infection is confirmed by testing for virus in the blood with an HCV-RNA. National recommendations (Health Resources and Services Administration) are to screen all persons with HIV/AIDS for chronic hepatitis B and C infection. Those who are negative should have repeated screening yearly.

3. A 51-year-old man with HIV/AIDS comes to clinic complaining of weight gain. He has a body mass index (BMI) of 31 kg/m². Control of his HIV infection is documented with a CD4 count of 520 cells/mm³ and an undetectable HIV viral load. On exam, there is a fat deposit (buffalo hump) over his upper dorsocervical spine, abdominal obesity, but slender-appearing arms and legs. Clinical considerations should include:

- A. Uncontrolled HIV infection causing wasting
- B. Normal aging

- C. Lipodystrophy with evidence of metabolic syndrome
- D. An eating disorder
- E. An inherited metabolic disorder

Answer: C HIV-associated lipodystrophy syndrome has four components: visceral fat accumulation (abdominal obesity), subcutaneous fat atrophy (slender arms and legs), atherogenic lipid profile, and glucose intolerance. The etiology of HIV-associated lipodystrophy has not been fully elucidated. However, dietary excess, chronic inflammation due to long-standing HIV infection, genetic predisposition, and the role of certain antiretrovirals may all play a role. The prevalence of metabolic syndrome has markedly increased in persons with HIV/AIDS and may predispose to accelerated cardiovascular disease. This patient should have fasting glucose and lipids checked and should be counseled on weight control and exercise.

4. A 42-year-old woman with HIV/AIDS presents with diarrhea. This has been going on for at least 2 months and is associated with mild abdominal cramping and weight loss because eating increases her cramps and diarrhea. She denies fevers or vomiting. What information is most helpful in planning her evaluation?

- A. A family history of inflammatory bowel disease
- B. The presence of blood in the stool
- C. Obtaining a history of recent travel in the United States
- D. Her most recent CD4 cell count
- E. A history of lactose intolerance

Answer: D Diarrhea is very frequent among persons living with HIV/AIDS. The etiology of diarrhea is best predicted by a person's CD4 count. In those with a normal CD4 count, diarrhea is often related to medications, lactose intolerance, or irritable bowel syndrome. Usually, weight loss is not a significant component. When the CD4 count declines, opportunistic infections are more likely. At CD4 counts below 100 cells/mm³, enteric pathogens are common, including bacterial pathogens (*Salmonella*, *Shigella*, *Campylobacter*, *Clostridium difficile*, and enteroaggregative *Escherichia coli*) and parasites (*Cryptosporidium*, microsporidia). At CD4 counts below 50 cells/mm³, CMV, disseminated *Mycobacterium avium* complex (MAC), or AIDS enteropathy may cause diarrhea. The diagnosis can be made by stool cultures and smears for parasites, but both upper and lower GI endoscopy may be needed to obtain biopsies if stool examinations are negative.

5. A 52-year-old man with HIV/AIDS is seen in HIV clinic complaining of fatigue. When pressed, he admits to intermittent diarrhea and occasional fevers. He is on antiretrovirals. He is slender with a BMI of 20.3 kg/m². His examination is otherwise unremarkable except for a few raised cherry-colored nodules on his arms and chest. Which of the following could contribute to HIV-related wasting?

- A. Excessive exercising
- B. Inadequate dietary intake
- C. An opportunistic infection or uncontrolled HIV infection increasing his energy requirements
- D. AIDS enteropathy causing malabsorption
- E. All of the above

Answer: E HIV-associated wasting is multifactorial. A careful dietary history and evaluation by a nutritionist is important to ensure adequate caloric intake. Dietary energy requirements are increased in persons who exercise regularly or who have increased metabolic demands due to an opportunistic infection and/or uncontrolled HIV infection from resistant virus. Malabsorption due to disease of the small intestine or pancreatic insufficiency also increases dietary caloric requirements because a percentage of nutrients are not being absorbed. Symptoms of nausea, vomiting, or anorexia may further decrease needed caloric intake. **Laboratory Measurement Value Normal Range** Bilirubin 1.0 0.2-1.3 mg/dL Alkaline phosphatase 120 38-126 UL AST 80 5-34 UL ALT 90 0-55 UL Total protein 7.8 6.3-8.2 g/dL Albumin 4.0 3.5-5.0 g/dL

Ch / 391 **PULMONARY MANIFESTATIONS OF HUMAN IMMUNODEFICIENCY VIRUS AND THE ACQUIRED IMMUNODEFICIENCY SYNDROME**

1. Which of the following pulmonary complications is most likely in an HIV-infected person with a CD4 lymphocyte count above 500 cells/ μ L?

- A. *Streptococcus pneumoniae* pneumonia
- B. Disseminated *Mycobacterium tuberculosis*
- C. *Pneumocystis* pneumonia
- D. Pulmonary Kaposi sarcoma
- E. Lung cancer

Answer: A At a CD4 lymphocyte count above 500 cells/ μ L, HIV-associated complications such as *Pneumocystis* pneumonia (PCP) and pulmonary Kaposi sarcoma are unlikely. Among the remaining choices, *S. pneumoniae* pneumonia is more frequent than either disseminated *M. tuberculosis* (which less commonly presents with disseminated disease at a CD4 count above 500 cells/ μ L) or lung cancer.

2. *Pneumocystis* pneumonia may present with which of the following chest radiographic findings?

- A. Normal chest radiograph
- B. Focal consolidation
- C. Bilateral reticular or granular opacities
- D. Pneumatocoeles
- E. All of the above

Answer: E PCP can present with a wide range of chest radiographic findings, including all of the abnormal findings listed, as well as a normal radiograph.

3. A 40-year-old HIV-infected man presents to the emergency room with cough productive of purulent sputum and fevers for 2 days. He is homeless, smokes cigarettes, and has a history of alcohol abuse. He denies injection drug use and has never had pneumonia previously. He has not been on antiretroviral therapy (ART) nor antibiotic prophylaxis; his most recent CD4 T-cell count 3 months ago was 310 cells/ μ L. He has not been in health care contact since that time. He has no known drug allergies. On examination, he is alert and in no acute respiratory distress. His temperature is 38.4° C, blood pressure is 130/80, heart rate 95, respirations 15, and oxygen saturation of 96% on room air. His chest x-ray shows a right middle lobe consolidation. Which of the following should be recommended initially:

- A. Obtain a chest computed tomography (CT) scan with IV contrast.
- B. Initiate treatment with ceftriaxone and azithromycin.
- C. Initiate treatment with vancomycin and piperacillin/tazobactam.
- D. Initiate treatment with IV trimethoprim-sulfamethoxazole.
- E. Initiate treatment with isoniazid, rifampin, ethambutol, and pyrazinamide.

Answer: B The acute onset of illness with a focal opacity on chest radiograph is consistent with bacterial pneumonia, and the patient's history of cigarette smoking and alcohol abuse in addition to HIV infection increase his risk for bacterial pneumonia. The results of a chest CT are unlikely to influence initial treatment decisions in this case. Although opportunistic infections are possible, they are less likely because his CD4 count recently was over 200, and etiologies such as PCP or tuberculosis (TB) are less likely, given the acuity of symptoms and radiographic findings. He does not have risk factors for health care-associated pneumonia or known underlying lung disease, thus coverage for community-acquired pneumonia with ceftriaxone and azithromycin would be an appropriate first regimen.

4. You are asked to evaluate a 58-year-old HIV-infected man who was initially admitted to the hospital 15 days ago with fevers, chills, night sweats, weight loss, and cough. He has a history of TB treated 30 years ago. On admission, he was not on ART and was found to have a CD4 T-cell count of 10 cells/ μ L and an HIV viral load of over 100,000 copies/mL. A sputum induction was negative for acid-fast bacilli but positive for *Pneumocystis*. He was treated with trimethoprim-sulfamethoxazole, and after 8 days was improving. He was not given corticosteroids. He was then started on highly active antiretroviral therapy (ART) and discharged. He now presents with recurrent fever and increased dyspnea. His chest x-ray on admission showed faint bilateral, hazy air space opacities. Now 15 days later at his second hospitalization, his chest x-ray reveals increased dense bilateral air space opacities. What is the next most appropriate step in this patient's management:

- A. Start rifamycin, isoniazid, pyrazinamide, and ethambutol.
- B. Switch from trimethoprim-sulfamethoxazole to pentamidine.
- C. Stop HAART.
- D. Start Solu-Medrol.
- E. Bronchoscopy with bronchoalveolar lavage

Answer: E The differential diagnosis to consider in this patient who presents with worsening of respiratory symptoms and air space opacities includes inadequately treated or nonresponding PCP, a new opportunistic infection, a noninfectious process such as congestive heart failure, or immune reconstitution inflammatory syndrome (IRIS). Because his initial diagnosis of PCP was based on sputum induction, a bronchoscopy would be indicated to assess for other infections before diagnosing IRIS, which is ultimately what this patient was thought to have. He improved with the addition of a brief course of corticosteroids, completion of 21 days of trimethoprim-sulfamethoxazole, and continuation of his ART.

5. When should ART be started in an HIV-infected person with a new diagnosis of TB and a CD4 cell count below 50?

- A. After completion of TB treatment
- B. Within 2 weeks of starting TB treatment
- C. After 1 month of TB treatment
- D. When sputum cultures are no longer positive for TB
- E. When patient is no longer febrile

Answer: B Although initiation of ART used to be delayed until after TB therapy, owing to drug interactions and the concern for the immune reconstitution syndrome, several randomized studies have shown decreased mortality, greater AIDS-free survival, and more rapid conversion of sputum smears and culture with early initiation of ART. Thus, all HIV-infected individuals with TB should receive ART. If the patient is naïve to ART, it is recommended that ART be initiated within 2 weeks of TB treatment initiation in individuals with CD4 cell counts below 50 cells/ μ L and within 8 to 12 weeks in all others. Individuals receiving ART should continue its use during TB therapy.

Ch / 392 SKIN MANIFESTATIONS IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

1. All of the following skin conditions are increased in frequency and/or severity in patients with HIV/AIDS. Which one of them is clearly exacerbated (or unmasked) by initiation of antiretroviral therapy (ART) as an immune reconstitution manifestation?

- A. Seborrheic dermatitis
- B. Papular pruritic eruption (PPE) of HIV
- C. Malignant melanoma
- D. Atopic dermatitis
- E. Herpes zoster

Answer: E Herpes zoster has been one of the more commonly encountered diseases in the immune reconstitution inflammatory syndrome (IRIS) and typically appears during the second stage (≈3 months after initiation of ART). Other skin disorders in HIV-positive patients that manifest with worsening that is attributed to immune reconstitution include: human papillomavirus, reactivation of herpes simplex and cytomegalovirus, cutaneous mycobacterial infection, and molluscum contagiosum. The other choices listed are not known to be significantly exacerbated by initiation of ART; in fact, some of them show marked improvement with it.

2. Which of the following pruritic eruptions is **not** a skin disorder that is known to be increased in frequency and/or severity in AIDS patients?

- A. Secondary syphilis
- B. Prurigo nodularis
- C. Pityriasis rosea
- D. Seborrheic keratosis
- E. PPE

Answer: C Pityriasis rosea is an acute self-healing exanthem of unknown etiology for which many infectious agents have been incriminated. It is not known to be definitively associated with HIV/AIDS. Syphilis is frequently seen in patients with HIV infection: primary, secondary, and tertiary forms of syphilis may be manifested clinically as they are in HIV-negative individuals, but atypical findings are not uncommon. Prurigo nodularis is characterized by pruritic dome-shaped nodules that particularly develop in persons with background skin pigment and CD4 counts below 100 cells/mm². Seborrheic dermatitis and keratosis have a strikingly increased prevalence in HIV-infected patients. PPE is commonly seen in Africa and Asia in association with HIV. Skin biopsies are indicated to distinguish between PPE and other itchy papular eruptions in patients with HIV/AIDS. When present, PPE is highly predictive of HIV infection and is often the presenting sign.

3. Oral hairy leukoplakia is associated with which of the following infectious organisms?

- A. Epstein-Barr virus (EBV)
- B. *Candida*
- C. Herpes simplex
- D. Cytomegalovirus (CMV)
- E. *Cryptococcus*

Answer: A Oral hairy leukoplakia is characterized by nonpainful white plaques with a feathered edge, especially on the lateral borders of the tongue. It is associated with EBV and is very rare in immunocompetent hosts. There is no specific treatment for it, but it tends to resolve when patients are taking ART. Superinfection with *Candida* species should be considered if the lesions are painful.

Ch / 393 HEMATOLOGY AND ONCOLOGY IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

1. A 47-year-old man with a history of sex with men presents to a clinic complaining of a purplish 1.3-cm lesion on his left calf, fatigue, and intermittent sweats. Initial evaluation reveals a temperature of 38.3° C, positive serology for HIV, 246 CD4 cells/mm³, 1540 neutrophils/mm³, and hemoglobin of 8.6 g/dL. A skin punch biopsy of the calf lesion reveals Kaposi sarcoma (KS). Evaluation and care includes all of the following **except**:
 - A. cART with emtricitabine, tenofovir, ritonavir, and darunovir
 - B. A reticulocyte count
 - C. A blood test for C-reactive protein
 - D. A stool guaiac for occult blood
 - E. Recombinant erythropoietin to a target hemoglobin of greater than 10 g/dL.

Answer: E This patient presents with KS and symptoms suggestive of Kaposi sarcoma herpesvirus–associated Castleman disease (KSHV-MCD), including fever and severe anemia despite a relatively preserved CD4 count. Appropriate evaluation of anemia is indicated. This includes a reticulocyte count and evaluation for gastrointestinal blood loss. For patients in whom KSHV-MCD is suspected, C-reactive protein is an appropriate first test. Additionally, patients with HIV and KS should be started on combination antiretroviral therapy (cART). Erythropoiesis-stimulating agents were approved for use with zidovudine but not other cART. Given the risk of serious side effects from erythropoietin, especially when targeted to achieve hemoglobin levels that are close to normal, the decreased occurrence of anemia with newer cART, effective treatment of HIV-associated anemia with cART itself, and in this case the likelihood of an additional treatable cause of anemia (KSHV-MCD), erythropoietin would not be used.

2. A 35-year-old man presents with nausea, vomiting, fever, and weight loss. Computed tomography scan shows small bowel thickening with obstruction, adenopathy, and liver nodules. Biopsy from a small section of resected bowel shows Burkitt lymphoma. An HIV screening enzyme-linked immunosorbent assay (ELISA) is positive. CD4 count is 350 cells/mm³. Which medication or medications should **not** be administered as an initial part of therapy?
 - A. Allopurinol
 - B. cART with emtricitabine, tenofovir, ritonavir, and darunovir
 - C. Rituximab
 - D. Full-dose cyclophosphamide
 - E. Trimethoprim-sulfamethoxazole

Answer: B Patients with Burkitt lymphoma require full-dose chemotherapy including rituximab. Important supportive care includes prevention of tumor lysis syndrome with allopurinol, and trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis.⁸ Initiation of a ritonavir-based HIV regimen is not advised as an initial part of therapy owing to the CYP3A4 inhibitory activity of ritonavir and its effect on the pharmacokinetics of chemotherapy drugs needed for the treatment of Burkitt lymphoma.

3. A 47-year-old woman with HIV is found to have atypical squamous cells of undetermined significance on a Pap smear. CD4 count is 275 cells/mm³. Colposcopy reveals no abnormalities. What established intervention is appropriate and most likely to reduce the risk of development of squamous intraepithelial lesions (SIL).
 - A. A 3-month course of interferon-alpha
 - B. cART with emtricitabine, tenofovir, ritonavir, darunovir
 - C. PAP smears every 6 months for 3 years
 - D. HBV vaccine
 - E. Valacyclovir 1000 mg daily

Answer: B cART is associated with improved immune control of HPV, the etiologic agent of cervical cancer, and reduced risk of squamous intraepithelial lesions (SIL).³ Interferon-alpha is not indicated for CIN prevention. HBV vaccine prevents against hepatitis B and associated hepatocellular carcinoma. HIV-infected women are recommended to have Pap smears every 6 months for 1 year, then yearly thereafter if normal, *not* every 6 months for 3 years.

4. A 27-year-old African American man presents to an emergency room with right arm weakness. Physical exam is also remarkable for cachexia, oral candidiasis, and right lower extremity swelling. Brain magnetic resonance imaging shows three ring-enhancing masses with mass effect. A rapid HIV screen is positive. CD4 cell count is 5 cells/mm³. Which of the following are **not** indicated as part of the initial diagnostic evaluation?

- A. Lower extremity ultrasound
- B. Brain biopsy if it can be done safely
- C. 2 weeks of empirical pyrimethamine combined with sulfadiazine and leucovorin for possible toxoplasmosis, withholding definitive diagnostic tests during this period
- D. Lumbar puncture with evaluation of cerebrospinal fluid
- E. (18F)-fluorodeoxyglucose positron emission tomography

Answer: C AIDS patients with ring-enhancing brain masses need urgent evaluation to establish a correct diagnosis. Appropriate evaluation includes nuclear imaging of the brain, evaluation of cerebrospinal fluid, and biopsy if it can be done safely. In the cART era, empirical treatment of toxoplasmosis as a diagnostic tool is no longer indicated, although the use of pyrimethamine combined with sulfadiazine and leucovorin for possible toxoplasmosis while awaiting biopsy results is reasonable in some cases, especially in patients with positive toxoplasmosis serology. Cancer increases risk for thrombosis, and this patient also has evidence of a possible right leg deep vein thrombosis that requires evaluation with a lower extremity ultrasound.

5. A 55-year-old man with HIV infection who has had sex with men and has a past history of intravenous drug use is being evaluated by a primary care physician. He currently smokes about 10 to 15 cigarettes per day. His CD4 count is 175 cells/mm³. What is the most important intervention to reduce the risk of lung cancer?

- A. Smoking cessation intervention
- B. Quadrivalent HPV vaccine
- C. Empirical valganciclovir therapy for presumptive cytomegalovirus (CMV) infection
- D. Screening for HCV infection and treatment if found to have chronic hepatitis C
- E. Empirical trimethoprim-sulfamethoxazole and prednisone for *Pneumocystis jiroveci* pneumonia (PCP)

Answer: A Smoking cessation interventions are indicated for reducing the risk of lung cancer. Other common malignancies observed in patients with HIV that are also associated with smoking include oropharyngeal, cervical, anal, and liver cancer. Lung cancer is not associated with HPV or HCV. Lung cancer may be associated with chronic lung infections; however, empirical therapy for CMV or PCP is not established for the prevention of lung cancer.

1. The diagnosis of HIV-associated neurocognitive disorders relies on:

- A. Neuropsychological testing demonstrating an impairment in two ability domains at least 1.0 standard deviation below the mean for norms but no cognitive impairment in everyday function
- B. Defects in cognitive function resulting in even mild impairment of daily function
- C. Neuropsychological testing demonstrating more than 2.0 standard deviations in at least two cognitive domains
- D. Sufficient factors demonstrate that impaired memory makes reading difficult.
- E. Abnormalities on brain neuroimaging, with head CT and T2-weighted images and fluid-attenuation inversion recovery (FLAIR) sequences by MRI as determined by standardized criteria for the diagnosis

Answer: A Although HAND may be suspected by the patient's complaints, the cognitive impairment is typically subtle because it does not affect day-to-day function. Therefore, HAND is best diagnosed by employing formal neuropsychological testing. Imaging studies are important adjunctive diagnostic tests and also useful for follow-up but by themselves do not make the diagnosis.

2. Factors that may contribute to the development of HIV dementia include **all but one** of the following:

- A. *APOE4* heterozygosity
- B. Age
- C. Profound immunosuppression
- D. Prior substance or alcohol abuse
- E. Race

Answer: E A wide variety of factors have been associated with HIV dementia. It is more likely in the setting of *APOE4* heterozygosity, advanced age, profound immunosuppression, and prior substance and alcohol abuse. However, there is no evidence that any particular race is more or less likely to be affected when one controls for other factors.

3. A common early complaint of individuals affected by HIV-dementia is:

- A. Headache
- B. Seizures
- C. Difficulty reading
- D. Paresthesias
- E. Getting lost in familiar environments

Answer: C The inability to recall what one has just read is a common complaint among persons with early HIV dementia. This complaint is likely the result of impaired concentration and poor memory. Although headaches are reported, they correlate poorly with HIV dementia. Seizures occur rarely and usually, like the complaint of getting lost in familiar environments, in more advanced disease. Paresthesias are generally the consequence of an associated peripheral neuropathy.

4. A feature that distinguishes HIV myelopathy from many of the other causes of HIV-associated myelopathy (e.g., lymphoma, varicella-zoster myelitis) is:

- A. Spasticity of the lower extremities
- B. Imbalance and gait disturbance
- C. Sphincter dysfunction
- D. The absence of a discrete sensory level over the trunk to pinprick
- E. Babinski signs

Answer: D Unlike many of the other myelopathies that occur with HIV infection, HIV vacuolar myelopathy does not exhibit a discrete sensory level over the trunk. The presence of such a level should suggest another etiology of the spinal cord disorder.

5. All but one of the following statements regarding peripheral neuropathy associated with AIDS is true:

- A. Many of the medications used in the treatment of AIDS can result in a clinically identical peripheral neuropathy.
- B. A demyelinating peripheral neuropathy resembling Guillain-Barré syndrome or chronic inflammatory peripheral neuropathy may be observed shortly after initial infection.
- C. Peripheral neuropathy is the most common neurologic abnormality observed in patients with HIV infection.
- D. Skin biopsy with examination of the cutaneous nerves may be helpful in establishing the diagnosis.
- E. Recovery from HIV-associated peripheral neuropathy often follows the use of effective antiretroviral therapy.

Answer: E Although symptomatic therapy is often helpful for the pain and paresthesias that occur with HIV-associated peripheral neuropathy, reversal of the disorder is virtually unheard of. In addition to many antiretroviral therapies, particularly, the “d” drugs, other therapies frequently employed in patients with AIDS (e.g., isoniazid, thalidomide) may cause a clinically similar peripheral neuropathy.

Ch / 395

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME IN HIV/AIDS

1. A major risk factor for developing paradoxical tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) is:

- A. Starting antiretroviral therapy (ART) in a patient with a low CD4+ T-cell count
- B. Starting ART in a patient with a high CD4+ T-cell count
- C. Starting ART in a patient with pulmonary TB
- D. Starting a protease inhibitor-containing regimen
- E. Starting ART in a patient with rifampin-resistant TB

Answer: A TB-IRIS has been associated with a low CD4+ T-cell count (usually < 50/μL) in several studies, probably because it is a marker of a high pathogen load and an increased susceptibility to restoration of a pathogen-specific immune response that causes immunopathology. All ART regimens may cause TB-IRIS, and TB-IRIS may develop in patients with all types of TB, including patients with multidrug-resistant TB.

2. Which of the the following statements is correct?

- A. In an HIV-infected patient with cryptococcal meningitis, ART should be started within 2 weeks after the start of the cryptococcal treatment.
- B. In an HIV-infected patient with cryptococcal meningitis, ART should be started at least 4 weeks after the start of the cryptococcal treatment.
- C. In an HIV-infected patient with cryptococcal meningitis and a CD4+ T-cell count below 50 cells/μL, ART should be started within 2 weeks after the start of the cryptococcal treatment.
- D. In an HIV-infected patient with cryptococcal meningitis and very few leucocytes in the cerebrospinal fluid (CSF), ART can be started together with the start of the cryptococcal treatment.

Answer: B Commencing ART within the first 2 weeks after starting cryptococcal meningitis treatment is associated with increased mortality compared with starting ART at least 4 weeks after the start of the cryptococcal treatment. The presence of very few leukocytes in the CSF is a further risk factor for developing cryptococcal IRIS.

3. Which of the the following statements is correct?

- A. All patients with IRIS should be treated with prednisone.
- B. Patients with IRIS should never be treated with prednisone.
- C. In patients with IRIS, ART should be stopped.
- D. In patients with TB-IRIS, prednisone may be beneficial.

Answer: D The effectiveness of prednisone as treatment for IRIS varies from one type of IRIS to another. A randomized controlled trial in South Africa demonstrated that prednisolone therapy is a safe and effective treatment option for paradoxical TB-IRIS. For progressive multifocal leukoencephalopathy (PML)-IRIS, only early use of corticosteroid therapy may be effective. For Kaposi's sarcoma (KS)-IRIS, the benefits of corticosteroids are not established. Potential risks of using corticosteroid therapy in patients with HIV infection who are very immunodeficient should always be considered.

4. IRIS can be prevented by which one of the following?

- A. Early ART at a high CD4+ T-cell count
- B. Prophylaxis for opportunistic infections
- C. Early diagnosis and treatment of opportunistic infections
- D. All of the above

Answer: D Commencing ART at a high CD4+ T-cell count, as well as prophylaxis for opportunistic infections, will prevent the occurrence of opportunistic infections and therefore IRIS. Earlier diagnosis and treatment of opportunistic infections will reduce the pathogen load and therefore the risk of developing IRIS.

1. A 55-year-old woman has had gradually progressive weakness and numbness in her lower limbs. On examination, her right lower limb has spastic tone and 4-/5 strength diffusely. The left lower limb has normal tone and full power. Vibration and position sense are markedly impaired in the right lower limb, and pain and temperature perception are markedly impaired in the left lower limb. The remainder of the neurologic examination is normal. Where would you best localize her lesion?

- A. Brain stem
- B. Cerebral hemispheres
- C. Diencephalon
- D. Peripheral nervous system
- E. Spinal cord

Answer: E Neurologic examination findings confined to the lower limbs are highly suggestive of a spinal cord localization. The dissociated sensory abnormalities in this patient (impairment of vibration and position sense in the right lower limb and impairment of pain and temperature perception in the left lower limb), as well as the weakness and spastic tone in the right lower limb, all point to a hemisection of the right spinal cord at a midthoracic level, a so-called Brown-Séquard syndrome. Recall that there are two major somatosensory systems in the spinal cord: (1) the small-fiber pain and temperature system that courses in the contralateral anterolateral funiculus of the spinal cord and (2) the large-fiber vibration and position sense system that courses in the ipsilateral dorsal funiculus. The descending corticospinal tract courses in the ipsilateral lateral funiculus of the spinal cord. Lesions in the other structures listed are unlikely to produce this clinical picture.

2. A 70-year-old woman with hypertension and diabetes mellitus fell while getting out of bed and was brought to the emergency department by her daughter. CT scan of the brain shows a hemorrhage in the cerebellar vermis. Which of the following findings on neurologic examination is she most likely to have?

- A. An involuntary movement disorder
- B. Internuclear ophthalmoplegia
- C. Limb ataxia
- D. Lower limb spasticity
- E. Truncal ataxia

Answer: E The cerebellum is the major brain structure involved in coordinating limb and trunk movements. It does this by comparing the present position of the limbs and trunk with the intended movement. The cerebellar hemispheres coordinate the limbs, and the cerebellar midline vermis coordinates the trunk. Hence, a hemorrhage in the cerebellar vermis, likely hypertensive in origin, is most likely to produce truncal ataxia (inability to stand upright with eyes open). Involuntary movement disorders usually arise from basal ganglia lesions. Internuclear ophthalmoplegia (inability to adduct one eye with horizontal gaze) is seen with brain stem lesions that involve the medial longitudinal fasciculus. Lower limb spasticity is seen with lesions of the corticospinal tracts and is most likely due to a spinal cord lesion.

3. A 24-year-old woman abruptly became unresponsive and stared for about a minute. About 10 seconds later, she started rubbing her thighs rhythmically with her right hand for about a minute. She was confused afterwards for about 10 minutes, following which she was tired and had a mild headache for the rest of the day. What is the most likely diagnosis?

- A. Absence seizure
- B. Focal seizure with dyscognitive features
- C. Migraine with aura
- D. Myoclonic seizure
- E. Syncope

Answer: B A focal seizure with dyscognitive features (formerly classified as a complex partial seizure) typically originates in the temporal lobe and involves limbic circuits. The amygdala and hippocampus, which are the major components of the limbic system, are located in that lobe. During a focal seizure with dyscognitive features, consciousness is impaired and the patient manifests automatisms (e.g., rubbing the thighs rhythmically). The confusion following the spell represents the postictal state, which is often seen following partial seizures. Absence seizures are seen in children and consist of several seconds of unresponsiveness and eye blinking without postictal confusion. Migraine with aura rarely causes unresponsiveness, and rhythmic limb movements would be most unlikely. Myoclonus is a brief irregular jerk of a limb and can be seen with juvenile myoclonic epilepsy; the movement described in this vignette is too prolonged for myoclonus.

4. A 60-year-old man has noted difficulty walking for the past 4 days. He recently lost 20 pounds from dysphagia as a complication of radiation treatment for tongue cancer. On examination, he has weakness of right ankle dorsiflexion and eversion. Right ankle inversion is normal. There is a patch of numbness on the dorsum of the right foot over the first web space. These findings suggest involvement of which of the following?

- A. Femoral nerve
- B. Lateral femoral cutaneous nerve
- C. Obturator nerve
- D. Peroneal nerve
- E. Tibial nerve

Answer: D The peroneal nerve innervates the anterior tibialis muscle, which causes ankle dorsiflexion, and the peroneal muscle, which causes ankle eversion. It also supplies sensation to the first web space of the foot. This nerve is commonly compressed at the fibular head, and rapid weight loss can facilitate compression at this site. The femoral nerve innervates the knee extensor muscles and supplies sensation to the anterior thigh. The lateral femoral cutaneous nerve supplies sensation to the anterolateral thigh and has no motor function. The obturator nerve innervates the thigh adductor muscles and provides sensation to the medial thigh. The tibial nerve innervates the plantar flexor muscles and supplies sensation to the sole of the foot.

5. A 60-year-old man sees his physician because of slowly progressive weakness in his limbs for the past 5 years. On examination, he has atrophy of the intrinsic muscles in his hands and feet. He is unable to walk on his heels and cannot make a tight grip with either hand. He has flaccid muscle tone, absent muscle stretch reflexes, and flexor plantar responses. He most likely has a lesion involving which of the following structures?

- A. Brain stem
- B. Cerebellum
- C. Cerebral hemispheres
- D. Peripheral nerves
- E. Spinal cord

Answer: D Muscle atrophy (especially of distal muscles), flaccid muscle tone, and areflexia are all highly suggestive of a lesion of peripheral nerves. A lesion to the brain stem usually results in cranial nerve abnormalities; cerebellar lesions typically cause ataxia of the trunk and/or limbs. Lesions to the cerebral hemispheres often produce visual field deficits and loss of higher cortical functions, such as aphasia (defect in production or understanding of language), apraxia (defect in performance of a complex motor task), and agnosia (defect in recognizing a complex sensory stimulus). A spinal cord lesion typically produces loss of motor and sensory function below the level of the lesion. Extensor plantar responses (Babinski sign) would be expected with lesions to the brain stem, cerebral hemispheres, and spinal cord.

1. Which of the following types of disorders may manifest with a combination of substantial intellectual deficits, mood symptoms, psychotic symptoms, and anxiety symptoms?

- A. Anxiety disorders
- B. Bipolar disorders
- C. Depressive disorders
- D. Neurocognitive disorders
- E. Psychotic disorders

Answer: D See Table 397-2. Although the hallmark of neurocognitive disorders is intellectual deficits, they often manifest with symptoms affecting other parts of the mental status examination, including mood, psychotic, and anxiety symptoms. Intellectual deficits consistent with delirium or dementia are not characteristic of anxiety, bipolar, depressive, or psychotic disorders.

2. After successful resolution of a first episode of major depression with antidepressant medication therapy, how long should the medication be continued?

- A. Not at all; discontinue as soon as the episode has resolved
- B. 1 week
- C. 1 month
- D. At least 4 to 8 months
- E. Indefinitely for lifelong maintenance therapy

Answer: D As noted in the section on treatment of major depression, continuation of treatment is required to prevent relapse into the depressive episode. The continuation phase should be at least 4 to 8 months, and some experts recommend up to 1 year. However, assuming the patient's symptoms remain in full remission at the end of the continuation phase, lifelong maintenance therapy is indicated only for patients with recurrent episodes of depression (and, some believe, for others at particularly high risk for recurrence or for the destructive effects of another depressive episode, e.g., late-onset depression, highly suicidal depression).

3. For patients who present with a major depressive episode, it is important to inquire about any prior history of hypomania, because such a history has which of the following implications for treatment?
- A. Need to treat all first-degree relatives prophylactically
 - B. Need to obtain informed consent from the nearest relative
 - C. More likely to respond to antidepressant medication
 - D. More likely to respond to psychotherapy
 - E. May require mood stabilizer treatment prior to antidepressant therapy

Answer: E Please see text regarding bipolar II disorder under "Other Mood Disorders." Antidepressant therapy in this condition may precipitate hypomania (or mania). At the least, extremely careful monitoring is required, and many experts recommend not starting antidepressant therapy at all until reevaluating the patient after institution of treatment with a mood stabilizer such as lithium or valproate.

4. Which of the following disorders has a pathophysiology that is probably mediated primarily by striatofrontal systems?
- A. Generalized anxiety disorder
 - B. Obsessive-compulsive disorder
 - C. Panic disorder
 - D. Posttraumatic stress disorder
 - E. Social anxiety disorder

Answer: B As discussed in the text under anxiety disorders and other disorders with prominent anxiety, obsessive-compulsive disorder has been reclassified separate from the anxiety disorders because of its differing pathophysiology. Post-traumatic stress disorder also has been classified separately (under trauma- and stress-related disorders), but its neurobiology appears to be more closely related to the anxiety disorders than to obsessive-compulsive disorder.

5. Which of the following predicts better longer-term outcome in schizophrenia?
- A. Absence of negative symptoms such as apathy and social withdrawal
 - B. Enduring family discord
 - C. Being male
 - D. Ongoing psychosocial stressors
 - E. Younger age of onset

Answer: A As discussed in the section on schizophrenia, each of factors B through E predicts a poorer outcome. Prominent negative symptoms predict a poorer course, as reflected in the poor response of negative symptoms to antipsychotic medications (hence the need for psychosocial rehabilitation programs in this condition). The absence of negative symptoms suggests higher functioning if the positive (psychotic) symptoms of the disorder can be controlled with medication.

1. A 30-year-old woman presents with frequent bilateral, non-throbbing headaches that cause photophobia, phonophobia, and nausea. The headaches worsen with activity. They occur 4 times monthly and last 24 to 48 hours. The most likely diagnosis is:
- A. Migraine
 - B. Tension-type headache
 - C. Hemicrania continua
 - D. Atypical facial pain

Answer: A The most likely diagnosis is migraine. If a headache is associated with both photophobia/phonophobia and nausea, the diagnosis cannot be tension-type headache. Hemicrania continua is usually unilateral, and although it can last for longer periods of time, it may have autonomic symptoms. Atypical facial pain is really not a diagnosis in this case, because there are migrainous features. (See Society HCCotIH. *The International Classification of Headache Disorders*. 3rd ed. [beta version]. *Cephalalgia*. 2013;33: 629-808.)

2. A 35-year-old woman presents with a unilateral headache over her right eye. She has associated tearing and redness of the eye with the pain. The headaches last 40 minutes and occur daily, usually in the evening. The correct diagnosis is:

- A. Paroxysmal hemicrania
- B. Cluster headache
- C. Hemicrania continua
- D. Acute glaucoma

Answer: B She has unilateral brief pain with two autonomic features that are diagnostic of cluster headaches. Although men are more likely to have cluster headache, women suffer from this type of headache as well. Paroxysmal hemicrania would be more brief, usually lasting less than 30 minutes. Hemicrania continua is longer lasting, and acute glaucoma would not be intermittent or occur only at a specific time.

3. A 25-year-old man has increasingly frequent headaches characterized by bilateral holocranial headache, photophobia, nausea, and rare vomiting. The headaches occur 25 days each month, and he is now using almost daily sumatriptan. The most likely diagnosis is:

- A. Chronic migraine
- B. Chronic migraine with medication overuse
- C. Chronic tension-type headache
- D. Chronic tension-type headache with medication overuse

Answer: B The most likely diagnosis is chronic migraine with medication overuse, because he has a headache more than 15 days per month and uses sumatriptan more than 3 days in a week. The headache may revert to episodic or chronic migraine when he reduces his daily acute rescue treatment. The headache is associated with nausea and rare vomiting, so it is not a tension-type headache.

4. A 30-year-old woman presents with chronic daily headache, pulsatile tinnitus, and episodic blurring of her vision. On examination she has papilledema. What evaluation would you perform?

- A. Magnetic resonance imaging (MRI) and lumbar puncture (LP)
- B. MRI, LP, and visual fields
- C. Computed tomography (CT)
- D. LP alone
- E. None of the above

Answer: B The MRI is required to look for any mass lesions and can often show venous sinus thrombosis. The LP must be done to not only be sure that the opening pressure is elevated but also that the cerebrospinal fluid itself is normal. Visual fields must be performed and monitored to prevent blindness; visual acuity testing alone is insufficient. CT scans are good for excluding mass lesions but are not adequate alone. LP alone without imaging is contraindicated. LP also may be contraindicated if the patient has an associated significant Chiari I malformation.

1. A 34-year-old otherwise healthy construction worker presents to your office with a 3-week history of low back pain. He does not recall any specific trauma. He denies pain or weakness in his legs. His examination is notable for a decreased right ankle tendon reflex compared with the left. The most appropriate next step is to:

- A. Order magnetic resonance imaging (MRI) of the lumbar spine
- B. Order an MRI of the lumbar and thoracic spine
- C. Order an electromyogram (EMG) of the right leg
- D. Prescribe 3 days of bed rest
- E. Prescribe PRN analgesics and physical therapy

Answer: E Uncomplicated acute low back pain, with or without radiculopathy, is generally self-limited. Imaging studies are unnecessary unless any of the red flags (see Table 400-3) are present. The American College of Physicians recommends MRI only in patients who have serious or progressive neurologic deficits, in whom a serious underlying condition is expected, or in whom surgery or epidural steroids are being considered.

2. Long-term disability owing to mechanical neck pain is associated with all of the following **except**:

- A. Tobacco use
- B. Age younger than 45 years
- C. More severe pain at the onset
- D. Tendency to somatization
- E. Employment requiring heavy lifting

Answer: B Patients younger than 45 years have less recurrence. Long-term disability is more common with obesity, low education level, tobacco use, high levels of pain at the onset, tendency toward somatization, job dissatisfaction, lack of availability of light-duty employment, and need to perform significant lifting at work.

3. All of the following are true statements regarding spinal stenosis **except**:

- A. The symptoms may be intermittent.
- B. There is a good correlation between canal diameter and symptoms.
- C. Pain is almost always present.
- D. MRI may be useful in localizing the site of stenosis.
- E. EMG is generally not useful except to evaluate comorbid conditions.

Answer: B Lumbar spinal stenosis can present with intermittent or persistent signs and symptoms referable to both cord and roots; axial neck or back pain is almost always present. There is, however, poor correlation between symptoms and the diameter of the canal. MRI can localize and quantify the severity of the stenosis. Computed tomography (CT) myelography, which provides the details needed for surgical treatment, is another alternative. EMG generally is not useful in the diagnosis of spinal stenosis except to assess possible comorbid conditions.

4. An 81-year-old man presents to your office with 2 months of moderately severe mid-back pain. In certain positions, the pain can radiate to his right lateral ribcage and even anteriorly toward his umbilicus. All of the following would support a diagnosis of myelopathy **except**:

- A. Sensation of tingling in his left leg
- B. Weakness of both legs
- C. Difficulty with urinary incontinence
- D. Depressed reflexes in his right leg
- E. Positive Babinski reflex in his left leg

Answer: D Although there may be decreased reflexes in an acute myelopathy, reflexes would usually be increased in a chronic myelopathy of 2 months' duration. In this case, the presence of radicular pain helps with localizing a level but does not eliminate the possibility of a comorbid myelopathy.

5. Metabolic myelopathies have been associated with all of the following **except**:

- A. Vitamin A deficiency
- B. Vitamin B12 deficiency
- C. Vitamin E deficiency
- D. Copper deficiency
- E. None of the above

Answer: A Metabolic myelopathies can be caused by a deficiency in vitamin B12, vitamin E, and copper. Vitamin A deficiency is most commonly associated with blindness, xerophthalmia, poor bone growth, dermatologic problems, and impaired immune function.

Ch / 401

REGIONAL CEREBRAL DYSFUNCTION: HIGHER MENTAL FUNCTIONS

1. Episodic declarative memory is a cognitive function most closely associated with what brain region?

- A. Hippocampal formations
- B. Primary visual cortex
- C. Supplementary motor areas
- D. Putamen
- E. Hypothalamus

Answer: A The hippocampal formations are the anatomic locus of encoding new information, the necessary first step in creating new memories for facts or events. The other regions play much more peripheral roles in episodic declarative memory.

2. All of the following are commonly seen in the syndrome of transient global amnesia **except**:

- A. Impaired recall of events
- B. Brief loss of consciousness
- C. Preserved ability to speak
- D. Preserved ability to walk

Answer: B Loss of consciousness is not a feature of transient global amnesia. If a spell of impaired recall occurred in conjunction with loss of consciousness, other diagnoses such as a seizure disorder or syncope would be more likely.

3. Which brain region is most closely associated with comprehension of spoken language?

- A. Dominant prefrontal cortex
- B. Dominant inferior frontal lobe
- C. Nondominant inferior parietal lobe
- D. Dominant inferior parietal lobe
- E. Dominant hippocampal formation

Answer: D The dominant inferior parietal lobe is the region most closely linked to auditory comprehension.

4. The syndrome of hemispatial neglect refers to:

- A. Lack of awareness of one's own distorted speech
- B. Lack of awareness of objects in the hemispace contralateral to a perisylvian (frontotemporal-parietal) lesion
- C. Lack of awareness of objects in the hemispace ipsilateral to a perisylvian (frontotemporal-parietal) lesion
- D. Weakness in limbs contralateral to a perisylvian (frontotemporal-parietal) lesion

Answer: B Hemispatial neglect occurs in the visual hemispace contralateral to perisylvian lesions. Lack of awareness of impaired speech, such as occurs in Wernicke's aphasia, is a form of loss of awareness of one's deficits, but not of hemispatial neglect. Weakness per se is not a manifestation of hemispatial

neglect, although persons with nondominant hemisphere perisylvian lesions often experience anosognosia for their weakness.

5. All of the following may be seen with injury to the frontal lobes **except**:

- A. Apathy (abulia)
- B. Lack of energy
- C. Impulsiveness
- D. Lack of regard for the feelings of others (loss of empathy)
- E. Cortical blindness

Answer: E Cortical blindness is a manifestation of lesions in the occipital lobe. All of the other symptoms are ones seen in lesions in the frontal lobes.

Ch / 402 ALZHEIMER DISEASE AND OTHER DEMENTIAS

1. Which of the following features distinguishes the syndrome of mild cognitive impairment from dementia?

- A. Degree of impairment in daily activities
- B. Extent of anomia
- C. Age
- D. Degree of hippocampal atrophy

Answer: A By definition, persons with cognitive impairment are diagnosed with mild cognitive impairment if they are largely independent in daily affairs, whereas persons whose cognitive impairment makes them dependent on others are diagnosed with dementia. Although the severity of cognitive impairment is clearly correlated with the impairment in daily affairs, the level of cognitive impairment per se should not be used to distinguish mild cognitive impairment from dementia.

2. All of the following are true statements about the epidemiology of dementia due to Alzheimer disease **except**:

- A. The prevalence doubles every 5 years after age 65.
- B. Family history of dementia is a risk factor for Alzheimer disease dementia.
- C. Women are more than 3 times more likely to be affected than men.
- D. There are no geographic regions with exceptionally high prevalence.

Answer: C Although there are more women than men with dementia, owing to lower survival in men after the age of 65 years, there is no difference in the age-adjusted prevalence between men and women.

3. Which of the following would be the most specific and sensitive indicator that cerebrovascular disease was the cause of a patient's cognitive impairment?

- A. A diagnosis of hypertension
- B. Bilateral infarcts in thalamus on magnetic resonance scan
- C. A single infarct in the cerebellum
- D. Family history of dementia
- E. Sparing of learning and memory

Answer: B Bilateral infarcts in the thalamus are highly likely to cause cognitive impairment, including aphasia or amnesia. The other features have no relationship or only a weak relationship to cerebrovascular disease.

4. Which of the following is **not** a diagnostic feature of dementia with Lewy bodies?

- A. Parkinsonism
- B. Rapid eye movement (REM) sleep behavior disorder
- C. Visual hallucinations
- D. Unexplained frequent falls
- E. Cerebellar ataxia

Answer: E Cerebellar ataxia is not a feature of dementia with Lewy bodies.

5. You are asked to see an 80-year-old man who has parkinsonism, dementia, prominent visual hallucinations, dream enactment behavior, and urinary incontinence. Which of the following would be likely to occur with treatment of the urinary incontinence with an anticholinergic medication?

- A. Worsening of parkinsonism
- B. Exacerbation of nocturnal dream enactment behavior
- C. Increased confusion
- D. Diarrhea

Answer: C Anticholinergic medications, even if they claim not to cross the blood-brain barrier, can cause increased confusion. The other symptoms are unlikely to be a result of anticholinergic medications.

Ch / 403 THE EPILEPSIES

1. Which of the following is correct about the definition of seizures and epilepsy?

- A. Seizures and epilepsy are synonymous, therefore any person who has seizures can be diagnosed as having epilepsy.
- B. People who develop seizures owing to acute factors such as alcohol withdrawal or metabolic derangements can be diagnosed as having epilepsy if they occur on more than one occasion.
- C. Epilepsy is characterized by two or more unprovoked seizures (without apparent cause) occurring more than 24 hours apart.
- D. Only specific types of seizures, such as generalized tonic-clonic or absence seizures, qualify for establishing the diagnosis of epilepsy.
- E. All seizures should be treated with antiepileptic drugs.

Answer: C Epilepsy is characterized by an enduring predisposition of the brain to generate seizures, and it is defined clinically by two or more unprovoked epileptic seizures of any type occurring more than 24 hours apart. Seizures and epilepsy are not synonymous. Many acute brain insults can produce seizures (known as acute provoked seizures) without denoting the presence of epilepsy. These acute provoked seizures can recur if the acute provoking factor is repeated, they usually respond to treatment of the underlying cause, and they do not require antiepileptic drug treatment.

2. Which of the following is correct about the incidence and prevalence of epilepsy?

- A. About 1 in 26 people in developed countries can be expected to develop epilepsy during their lives, and the risk is higher in men than in women.
- B. Epilepsy is equally frequent in persons of any socioeconomic status and living in any region of the world.
- C. Risk factors for epilepsy can be identified in the majority of people who develop epilepsy.
- D. Most people who develop epilepsy have developmental abnormalities of the brain.
- E. About 1 in 200 people develop a seizure at some point in their lives.

Answer: A Epilepsy is one of the most common neurological conditions seen in general practice. Population studies in developed countries show that the lifetime risk of developing epilepsy is about 1 in 21 men and 1 in 28 women (1 in 26 overall). The risk is higher in developing countries and for individuals of lower socioeconomic status. Risk factors for epilepsy can be identified in only about 30% of persons with epilepsy, and the most common causes in adults are head injury, infections, stroke, and dementia. About 1 in 10 persons can be expected to have a seizure at some point in their lives.

3. Which of the following is **not** correct about the diagnosis of epilepsy?

- A. The diagnosis of epilepsy is made by a careful clinical history to determine whether the events in question are seizures and whether 2 or more have occurred more than 24 hours apart.
- B. Although an increasing number of genes have been linked to epilepsy, genetic testing of patients with epilepsy is indicated only in selected clinical conditions.
- C. Investigations such as electroencephalogram (EEG) and magnetic resonance imaging (MRI) are often necessary to determine the type of epilepsy syndrome and guide treatment.
- D. The absence of epileptiform discharges on a routine EEG casts serious doubts on the diagnosis of epilepsy.
- E. Long-term video EEG monitoring is helpful to determine the type and number of seizures a patient is experiencing, as well as identify the focus of the origin of the seizure and whether it is amenable to surgical resection.

Answer: D The initial EEG is normal in up to 60% of people with epilepsy, so a normal EEG does not detract from the diagnosis of epilepsy. The diagnosis is established by a careful history comprising three elements: the clinical context, provoking factors, and a detailed description of the event. The EEG and MRI are essential to establish the type of epilepsy and epilepsy syndrome, which in turn guide treatment decisions and prognosis. Only selected conditions merit genetic testing for the purpose of management and counseling. Long-term video EEG is necessary to establish the diagnosis in situations in which the clinical history is ambiguous, to determine the type and number of seizures the patient is having, and especially to identify the seizure focus in the brain and whether it can be safely resected surgically.

4. Which of the following is **not** correct about the treatment of epilepsy?

- A. About two thirds of patients with epilepsy are well controlled with one antiepileptic drug, but those who fail two antiepileptic drugs have a low chance of being controlled with further drug trials and are considered pharmacoresistant.
- B. The type of seizure and epilepsy syndrome determine which antiepileptic drug should be used to treat an individual patient.
- C. Antiepileptic drugs with a broad spectrum of efficacy against many types of seizures include valproate and levetiracetam, but some drugs like carbamazepine can exacerbate absence seizures.
- D. Valproate carries a high risk of major congenital malformations and poor intellectual development in children exposed to this medication in utero, so it should be avoided during pregnancy if possible.
- E. Newer antiepileptic drugs are more effective than older drugs.

Answer: E Although at least a dozen new antiepileptic drugs have been developed in recent years, they are no more effective than older drugs such as phenytoin, valproate, or carbamazepine. For example, in children with absence epilepsy, ethosuximide and valproate are more effective than the newer drug lamotrigine. Valproate, levetiracetam, lamotrigine, and topiramate have a broad spectrum of efficacy against focal and generalized seizures. Fortunately, most patients are well controlled with the first antiepileptic medication if it is appropriately chosen. However, because a lack of response to the first two antiepileptic drugs entails a poor prognosis, these patients are considered drug resistant. Although several drugs have risks of fetal malformations, valproate has the highest risk and also produces enduring deleterious effects on the intellectual development of children exposed in utero. Valproate should be avoided during pregnancy if at all possible. If it must be used, the lowest possible dose is recommended because the teratogenic effect is dose dependent.

5. Which of the following is **not** correct about the surgical treatment of epilepsy?

- A. Brain surgery for epilepsy is safe and superior to medical therapy in patients with temporal lobe epilepsy.
- B. The benefits of surgery are enduring; over 50% of patients can be expected to remain entirely seizure free at 10 years.
- C. Only patients who have failed all first-line drugs and still have frequent seizures are eligible for surgery.
- D. Before considering surgery, clinicians should ensure that common causes of poor response to antiepileptic drugs, such as lifestyle issues, are addressed and that the patient is adherent to appropriate antiseizure medications.
- E. Various types of electrical stimulation of the nervous system, including deep-brain stimulation, may be beneficial for selected patients with drug-resistant epilepsy.

Answer: C Patients who have failed two adequate trials of antiepileptic drugs should be referred for an evaluation of epilepsy surgery. Early surgery, performed within 2 years of developing drug resistance, is vastly superior to medical therapy in patients with temporal lobe epilepsy, with a number needed to treat with surgery, as compared to medical therapy, to achieve seizure freedom of 2. The benefits of surgery persist at 5 and 10 years. About 65% of patients are free of seizures in the long term, as compared with only 8% with medical therapy. Surgery remains underused despite clear evidence of its safety and efficacy. Pseudoresistance to antiepileptic drugs is common and should be investigated thoroughly. The most common causes are an incorrect diagnosis of epilepsy, using the wrong drug, poor adherence, and lifestyle issues that increase the chance of seizures, such as sleep deprivation and excessive alcohol use. Novel surgical strategies include radiosurgery and electrical stimulation of the brain (e.g., thalamus, hippocampus, cerebral cortex) and the peripheral nervous system (e.g., vagus nerve, trigeminal nerve).

Ch / 404 COMA, VEGETATIVE STATE, AND BRAIN DEATH

1. What clinical sign differentiates between a minimally conscious state and a vegetative state?

- A: Blinking to threat
- B: Marked dysautonomia
- C: Abnormal brain stem reflexes
- D: Myoclonus status
- E: Tracking an examiner's hand

Answer: E The only sign that, when found consistently, indicates awareness is the ability to track an object. All other signs can be seen in both conditions.

2. A 70-year-old woman was found snoring and unresponsive by her husband. On arrival to the emergency department, she had marked anisocoria, ocular bobbing, extensor posturing, and irregular breathing with pooling secretions requiring intubation. The vital signs were normal, and she was afebrile. Her computed tomographic (CT) scan was normal. Routine laboratory tests including glucose and blood gases are unrevealing. What is a likely diagnosis?

- A. Embolus to the basilar artery
- B. Intoxication/poisoning
- C. Status epilepticus
- D. Meningoencephalitis
- E. Anoxic-ischemic encephalopathy

Answer: A Ocular bobbing, anisocoria, and extensor posturing points to a brain stem lesion. The computed tomographic (CT) scan can be normal in the early hours after presentation. An embolus to the basilar artery may be seen as a hyperdense CT lesion, but a CT angiogram is a better study. Intoxi-

cation is unlikely due to localizing findings. Anoxic-ischemic encephalopathy usually spares the brain stem. Meningoencephalitis would be highly unlikely in a nonfebrile, acutely comatose patient with new brain stem findings.

3. What observation precludes brain death examination?

- A. Core temperature of 36° C
- B. Systolic blood pressure of 100 mm Hg
- C. Preserved tendon reflexes and Babinski signs
- D. Leg withdrawal after noxious stimulus
- E. Extensor posturing

Answer: E Extensor posturing indicates preserved brain stem function. Generally, blood pressures above 100 mm Hg and core temperatures above 35° C do not influence the neurologic examination. Tendon reflexes, Babinski signs, and leg withdrawal (triple flexion) response can be generated at a spinal level without cortical input and can be preserved in brain dead individuals.

4. A locked-in syndrome is characterized by all the following signs *except*:

- A. Absent horizontal eye movements
- B. Present vertical eye movements
- C. Blinking on command
- D. Deafness
- E. Quadriplegia

Answer: D Locked-in syndrome damages the ventral portion of the pons, sparing structures above and below it. In most patients with a locked-in syndrome, consciousness is spared because the ascending reticular formation, which produces wakefulness, is located in the dorsal portion of the pons.

5. A patient presents to the emergency department in coma (intact brain stem findings and localization only to noxious stimuli; moaning). Vital signs are normal. The CT scan is normal. Arterial blood gases show a metabolic acidosis. Lactate and glucose levels are normal, as are measures of renal function. What additional laboratory test is needed?

- A. Serum anion and osmolar gap
- B. Serum ammonia level
- C. Serum thyroid level
- D. Serum cortisone level
- E. Blood cultures

Answer: A Acute lactate metabolic acidosis points to ingestion of salicylates or ethylene glycol. The other disorders generally do not cause a metabolic acidosis.

Ch / 405 **DISORDERS OF SLEEP**

1. Which of the following symptoms are clues to an underlying sleep disorder?

- A. Brief lapses in memory
- B. Excessive daytime sleepiness
- C. Insomnia
- D. Morning headache
- E. All of the above

Answer: E Sleep disruption can cause all of these symptoms, and all are common among individuals with disturbed nighttime sleep. An individual might be attuned to specific aspects of their lives and

perceive the disruption of sleep in different ways. Thus, the clinician can use these symptoms as an opportunity to further question aspects of sleep.

2. Hypersomnia can be caused by which of the following?

- A. Sleep deprivation
- B. Sleep apnea
- C. Medication
- D. Liver failure
- E. All of the above

Answer: E The symptom of hypersomnia, or excessive ability to fall asleep, may be created by a wide range of issues. The clinician can think of sleepiness in general categories of sleep deprivation, sleep disruption (external [toxin] or internal [brain issue]) disturbing the mechanism for wake or sleep, a disturbance of circadian timing, or misperception of fatigue.

3. The diagnosis of insomnia requires which of the following?

- A. Actigraphy
- B. History of difficulty of sleeping at night
- C. History of difficulty with sleep at night and daytime sequelae
- D. History of somnogenic substance use and daytime sequelae
- E. Polysomnography

Answer: C Insomnia is a clinical diagnosis best made by a detailed history that demonstrates difficulty with sleep and a resulting symptom of daytime impairment. No other laboratory data are needed to make the diagnosis, but other information may be helpful in determining the best therapy in selected cases. Most patients with insomnia do not need polysomnography, although actigraphy can be helpful in determining the patient's bedtime and wake schedule.

4. The diagnosis of a circadian rhythm disorder is best made by:

- A. Sleep diary
- B. Polysomnography
- C. Multiple sleep latency test
- D. Maintenance of wakefulness test
- E. None of the above

Answer: A The diagnosis of a circadian rhythm disorder is dependent upon the complaint of insomnia or excessive sleepiness that is persistent for more than 3 months and can be confirmed by a sleep log or actigraphy for at least 14 days. Unfortunately, polysomnography and the daytime studies do not help in making this diagnosis.

5. Rapid eye movement (REM) sleep behavior disorder, characterized by excessive muscle activity in REM sleep and dream enactment, is most likely a harbinger of:

- A. Alzheimer disease
- B. Conversion disorder
- C. Heart failure
- D. Parkinson disease
- E. Renal failure

Answer: D REM sleep behavior disorder has been linked to degenerative disorders known as synucleinopathies (Lewy body dementia, Parkinson disease, and multiple system atrophy). The symptoms of dream enactment may present more than 30 years prior to other symptoms of these degenerative disorders, and up to 80% of individuals with REM sleep behavior disorder develop one of the three. REM sleep behavior disorder also has been associated with other disorders, such as

narcolepsy, and with brain stem strokes, lesions, and tumors. However, it is not associated with the other disorders listed as answers.

Ch / 406

APPROACH TO CEREBROVASCULAR DISEASES

1. Which of the following conditions is associated with the highest population-attributable risk of stroke?

- A. Cigarette smoking
- B. Diabetes
- C. Hypertension
- D. Poor diet
- E. Sedentary lifestyle

Answer: C Each of the listed conditions and lifestyle factors is associated with an increase in the risk of stroke. Of these, hypertension has the highest population-attributable risk for stroke.

2. The left common carotid artery most commonly arises from which of the following structures?

- A. Right subclavian artery
- B. Innominate artery
- C. Aortic arch
- D. Left subclavian artery
- E. Thyrocervical trunk

Answer: C The left common carotid artery most commonly arises directly from the aortic arch. In some individuals, it may arise from the proximal portion of the brachiocephalic trunk ("bovine" anatomy).

3. Which of the following arteries is commonly the first intradural branch of the internal carotid artery?

- A. Posterior communicating artery
- B. Ophthalmic artery
- C. Anterior choroidal artery
- D. Anterior cerebral artery
- E. Recurrent cerebral artery (Heubner)

Answer: B The ophthalmic artery may rarely arise from the carotid siphon, but it is generally the first branch after the internal carotid artery pierces the dura, followed by the posterior communicating artery and the anterior choroidal artery. The recurrent cerebral artery is generally a branch of the anterior cerebral artery.

4. Which of the following equations describes the normal cerebral autoregulatory relationship (CBF, cerebral blood flow; CVR, cerebral vascular resistance; MAP, mean arterial pressure)?

- A. $CVR = MAP - CBF$
- B. $MAP = CBF - CVR$
- C. $CBF = MAP/CVR$
- D. $MAP = CVR - CBF$
- E. $CBF = CVR/MAP$

Answer: E If MAP is decreased, there is a compensatory decrease in CVR (through dilation of cerebral arterioles) to maintain CBF constant. If MAP is increased, there is a compensatory increase in CVR (through constriction of cerebral arterioles). In the setting of ischemia, cerebral arterioles are maximally dilated; decreased MAP leads to a reduction in CBF to ischemic brain.

Ch / 407 **ISCHEMIC CEREBROVASCULAR DISEASE**

1. A patient complains of impaired vision in his left eye and has a left arm weakness. Examination shows a superior temporal visual defect in his left eye, and a cholesterol plaque is seen in his left eye on ophthalmoscopy. He has a left lower facial paresis and weakness in his left arm. Which of the following is the most likely cause of the stroke?

- A. Stenosis of the left carotid artery
- B. Stenosis of the left anterior choroidal artery
- C. Right basal ganglia hemorrhage
- D. Stenosis of the left vertebral artery
- E. Embolism from the ascending aorta

Answer: E Two vascular territories are involved simultaneously: the left carotid artery supplies the left ophthalmic artery, but the left-sided weakness would not be explained by a stroke in the left carotid distribution.

2. Which of the following is a contraindication to treatment with intravenous tPA (tissue plasminogen activator) in a patient with an acute ischemic stroke?

- A. Ischemic stroke 1 year ago
- B. Blood pressure 170/85 mm Hg
- C. Intracerebral hemorrhage 4 years ago
- D. Prior treatment with intravenous tPA for acute stroke 1 year ago
- E. Pure motor stroke consistent with a “lacunar” syndrome

Answer: C A prior ischemic stroke within 3 months is a contraindication to tPA, but not a stroke a year ago. Patients cannot be treated with a systolic blood pressure above 185 mm Hg or diastolic blood pressure above 110 mm Hg that does not respond to antihypertensive treatment. Patients who received intravenous tPA for a prior stroke can be treated, as long as they are beyond the 3-month period. Patients with ischemic stroke in any vascular distribution can be treated. However, intravenous tPA is contraindicated in patients with a prior history of intracerebral hemorrhage.

Ch / 409 **PARKINSONISM**

1. You are observing a 55-year-old man who was diagnosed with Parkinson disease 3 years ago. On examination, he has symmetrical slowing of his limb movements and gait with bradykinesia, rigidity, postural tremor, and postural instability. Cognitive function is preserved, and eye movements are normal. He has been receiving gradually increasing doses of a levodopa preparation and is currently taking levodopa/carbidopa 800/200 mg per day. He has noted clear benefit, but he has facial dystonic movements and additional wearing off between doses. At peak benefit, he has a soft voice that is somewhat difficult to understand; he has a great deal of difficulty with a variety of activities of daily living and has had to start using a cane because of the tendency to fall. Which of the following options should be considered at this time?

- A. Add an anticholinergic drug such as trihexyphenidyl 2 mg tid.
- B. Add a dopamine agonist such as pramipexole increasing to 1.5 mg tid.
- C. Add a cholinesterase inhibitor such as donepezil 5 mg bid.
- D. Obtain a magnetic resonance imaging (MRI) study including T2* or GRE sequences.
- E. Refer him to a surgical program for consideration of subthalamic nucleus deep brain stimulation.

Answer: D This patient’s disability has progressed too rapidly for typical Parkinson disease. He has no resting tremor, no asymmetry of symptoms, and early postural instability. His response to levodopa is relatively poor, and levodopa-induced dyskinesias are limited to facial dystonia. These features are strongly suggestive of an atypical parkinsonism, such as multiple system atrophy. In support of

multiple system atrophy, it would be extremely important to assess for evidence of autonomic dysfunction on his history and physical examination, including orthostatic hypotension, erectile dysfunction, and bladder incontinence. None of the treatment options outlined would be appropriate. Anticholinergics are largely effective for resting tremor. There is no evidence in this situation that a dopamine agonist would provide greater benefit than levodopa, and it may be more poorly tolerated, especially if he has problematic orthostatic hypotension. Cholinesterase inhibition is largely used for cognitive dysfunction in Parkinson disease; although it has been suggested that gait disturbances and postural instability may benefit from this treatment, such benefit has not been shown in the atypical forms of parkinsonism. Deep brain stimulation would not be expected to benefit symptoms that are not responding to levodopa. MRI scanning may provide support for the diagnosis of multiple system atrophy, including putamenal atrophy and evidence for iron deposition in putamen on T2* or GRE sequences.

2. A 55-year-old lawyer presents with right arm resting tremor, mild slowing and fatiguing on the performance of rapid repetitive movements, increased tone in his right arm with activation of the left, and reduced right arm swing but normal stride and postural stability. His writing is a bit smaller than before, and he is having mild difficulty using his computer mouse and performing tasks requiring fine dexterity in the right hand. His left side is entirely normal. Which therapy (with titration as necessary) would not be considered appropriate at this time?
- A. Levodopa/carbidopa 100/25 mg tid
 - B. Rasagiline 1 mg/day
 - C. Ropinirole 5 mg tid
 - D. Stalevo 100 mg tid
 - E. Pramipexole prolonged release 3 mg/day

Answer: D The patient's symptoms are mild but bothersome and justify initiation of therapy. Rasagiline is the least effective of all the agents listed, but it may provide mild benefit and is easy to use and well tolerated. Dopamine agonists are associated with fewer motor complications than levodopa, particularly dyskinesias, but they are less efficacious and have important side effects that must be monitored carefully, including excessive daytime sleepiness and impulse control disorders. Levodopa is the most effective treatment for Parkinson disease, and it is a reasonable choice even in the earliest stages if symptoms are interfering with quality of life. Stalevo is a combination preparation of levodopa/carbidopa/entacapone. In the early stages of disease, this treatment does not provide an advantage over levodopa and may be associated with more dyskinesias. The main indication for Stalevo is predictable wearing off of benefit with levodopa.

3. A 46-year-old woman has had Parkinson disease for the past 5 years. She is taking levodopa/carbidopa 150/37.5 mg every 3 hours as well as pramipexole 1 mg three times per day. At the peak benefit of levodopa, she functions near-normally but still has generalized dyskinesias that are occasionally bothersome to her. About 15 to 20 minutes before each dose of levodopa, she begins to notice a return of her tremor and hand clumsiness as well as occasional shuffling of gait and rare freezing. It takes approximately 30 minutes for the benefit of the next dose to "kick in," and occasional doses of levodopa do not seem to work. Which of the following treatment options would be most appropriate?
- A. Switch the immediate-release pramipexole to the extended-release formulation in the same dosage.
 - B. Switch the immediate-release to the controlled-release levodopa/ carbidopa preparation.
 - C. Switch the levodopa/carbidopa preparation to Stalevo 175 mg every 3 hours.
 - D. Add selegiline 5 mg/day.
 - E. Refer to a surgical program for consideration of deep brain stimulation.

Answer: E This young patient who retains an excellent response to levodopa but with problematic motor fluctuations is an ideal candidate for deep brain stimulation. Extended-release formulations of dopamine agonists usually are no more effective for motor fluctuations than are the immediate-

release preparations. Controlled-release formulations of levodopa are less bioavailable than immediate-release preparations and would likely worsen some of the unpredictability that she has in her responses. Additional entacapone, particularly with higher doses of levodopa, would likely worsen the dyskinesias, although the amount of off-time might improve. Selegiline would likely provide only minimal or mild benefit, particularly at this lower dose.

4. A 75-year-old woman has had Parkinson disease for 15 years. She continues to obtain benefit from levodopa, but even at the peak response she requires assistance for many tasks, uses a walker for ambulation, and has bothersome dyskinesias. She takes a levodopa preparation every 4 hours while awake. Each dose lasts approximately 3 hours, at which time her tremor can become bothersome and she has more difficulty in walking. Her short-term memory has declined, and she is occasionally confused. She comments on seeing people that she does not recognize in the dining room or children in the branches of the tree outside her kitchen. Which of the following treatments might be considered in the management of some of her problems?

- A. Amantadine
- B. Clozapine
- C. Pramipexole
- D. Risperidone
- E. Trihexyphenidyl

Answer: B Clozapine may be beneficial for several of this woman's symptoms, including hallucinations, bothersome off-period tremor, and dyskinesias. Amantadine, pramipexole, and trihexyphenidyl would be contraindicated, given her cognitive difficulties and the presence of hallucinations. Risperidone is also contraindicated in Parkinson disease because it can worsen the underlying parkinsonism.

5. A 65-year-old man has been diagnosed with Parkinson disease for 8 years. Which of the following clinical features would not be compatible with this diagnosis?

- A. A drop in systolic blood pressure of 30 mm Hg and diastolic blood pressure of 15 mm Hg from lying to standing
- B. A prominent postural and action tremor but no resting tremor
- C. Inability to obtain an erection for the past 3 years
- D. Frequent falls, particularly triggered by freezing of gait
- E. A wide-based gait and complete inability to perform tandem walking

Answer: E Patients with Parkinson disease can develop disabling autonomic dysfunction, including orthostatic hypotension and erectile dysfunction. These symptoms generally are not present or problematic early in the disease. Falls become a problem after several years of disease, but they also are not an early manifestation. Many patients with Parkinson disease do not have a resting tremor, but most of these will have a postural and action tremor. Even when patients with Parkinson disease have postural instability, they tend to walk on a narrow base and can perform tandem walking unless they are extremely unstable. This latter feature suggests additional cerebellar disease and may be supportive of a diagnosis of multiple system atrophy.

1. A 49-year-old woman presents with a 5-year history of involuntary pulling of her head toward the right shoulder. At times the movement has a tremulous or jerky component. The involuntary movement is associated with pain in the muscles in the back right side of the neck. The neck movements are interfering with her daily activities, particularly attending meetings, reading, watching television (she prefers to lie down for the latter), and driving. Initially she found that lightly touching the left side of her face or chin would allow her to keep her head in the mid-position, but this

maneuver has become less effective recently. She has no other neurologic complaints. Past and family histories are unremarkable, and she denies use of any prescription medications. On examination, she has rotation and tilting of her head to the right shoulder. She is unable to maintain her head in the midline for more than 15 seconds, and when asked to allow the head to take on its preferred position it rests on the shoulder with near 90-degree rotation and significant tilting. She also demonstrates a mild postural and action tremor in her hands. The remainder of the examination it is unremarkable. Which of the following statements is false?

- A. The history and clinical examination are typical of idiopathic adult-onset cervical dystonia.
- B. Genetic testing, including assessment of mutations in the *torsin A* and *THAP1* genes, would be negative and are generally not indicated.
- C. Deep brain stimulation would not be considered appropriate given the very focal nature of the dystonia.
- D. Botulinum toxin A injections would be considered appropriate as the first line of therapy.
- E. Drug history is important to elicit in such patients given the potential for tardive dystonia to manifest this phenotype.

Answer: C This patient has typical idiopathic cervical dystonia. Genetic testing is generally unremarkable and largely unnecessary unless there are other clinical clues to an alternative diagnosis. Botulinum toxin A remains the mainstay of therapy and is generally the treatment of choice unless the neck movements are extremely variable and complex and do not lend themselves to the benefit of weakening selected muscles, in which case medical therapy might be chosen initially. Tardive dystonia due to dopamine receptor blocking drugs (antipsychotics, some antiemetics) can result in a phenotype identical to that of idiopathic cervical dystonia, although a retrocollis pattern may be more common and other movements (e.g., orofacial dyskinesia), are not uncommonly also present. Deep brain stimulation of the globus pallidus has been shown in several studies to be very effective for medically refractory cervical dystonia.

2. You are seeing a 25-year-old student who has a long-standing history of jerky movements. These began when he was age 7 with excessive eye blinking. Symptoms have waxed and waned over the years and have included a variety of facial contractions such as nose wrinkling, jaw opening, head jerking, shoulder shrugging, hand shaking, contraction of abdominal and pelvic muscles, and leg kicking. When he was younger, he variably made sniffing or throat clearing sounds but never had spoken words or other vocalizations. His father has long-standing facial twitching and sniffing, and his mother has a tendency to obsessive-compulsive behavior. The patient has no history of behavioral or learning disabilities. He is an honors student and is considering applying for law school. The movements are having a negative impact on his social life, and he is concerned that they may interfere with his ability to interview successfully for law school. Which of the following statements is true?

- A. Behavioral therapy has a role to play in managing patients with this disorder.
- B. The description of the patient's movements is most compatible with multifocal myoclonus, probably due to "essential myoclonus."
- C. This syndrome constitutes a relatively rare disorder that is largely limited to the pediatric age group.
- D. Most patients with this disorder should be considered for early drug treatment to avoid the problems currently experienced by this patient.
- E. The absence of coprolalia or involuntary swearing makes it unlikely that his symptoms fulfill criteria for the diagnosis of Tourette syndrome.

Answer: A This patient fulfills the diagnostic criteria for Tourette syndrome. This common neuropsychiatric disorder typically begins in childhood and may remit in adolescence. However, it often persists to a greater or lesser extent in adulthood, and a small proportion of patients have symptoms beginning in adult life. Coprolalia is a relatively uncommon symptom. A large proportion of patients can be managed without drug therapy, which should be reserved for patients in whom tics are causing disability or impairing quality of life. Comorbid symptoms such as attention-deficit/hyperactivity disorder, obsessive compulsive disorder, and learning disabilities often are more

disabling than the tics themselves. Behavioral intervention, including habit reversal training, is a proven treatment.

3. Which of the following statements related to the neuroleptic drug-induced movement disorders is true?

- A. Acute dystonic reactions most often occur in elderly patients who receive atypical neuroleptics.
- B. Acute akathisia is an idiosyncratic side effect that generally resolves as the dose of the neuroleptic is increased.
- C. Neuroleptic malignant syndrome remains a severe and sometimes fatal complication of older typical neuroleptics, but newer atypical agents are largely devoid of this side effect.
- D. The introduction of atypical neuroleptics has clearly been associated with a reduced incidence of tardive dyskinesia.
- E. The first-line therapy of classic orobuccolinguomasticatory tardive dyskinesia is either trihexyphenidyl or benztropine 2 mg three times daily followed by reduction and if possible discontinuation of the causative neuroleptic.

Answer: D There has been a considerable reduction in the occurrence of tardive dyskinesia with the introduction of atypical neuroleptics, although these drugs still cause the problem to a lesser extent. Acute dystonic reactions occur more frequently in young patients who receive potent neuroleptic agents. Acute akathisia is often an early side effect that worsens in a dose-related fashion and resolves on withdrawal of the drug. Neuroleptic malignant syndrome remains an important complication of the atypical neuroleptics. Orobuccolinguomasticatory tardive dyskinesia typically worsens in response to anticholinergic drugs, which should be withdrawn in patients with problematic classic tardive dyskinesia. Conversely, these drugs are appropriate for the treatment of tardive dystonia, even though some patients develop more typical oral dyskinesias in response to them.

Ch / 411 **MULTIPLE SCLEROSIS AND DEMYELINATING CONDITIONS OF THE CENTRAL NERVOUS SYSTEM**

1. A definite diagnosis of multiple sclerosis can be made in which of the following clinically isolated syndromes in which no better explanation can be found:

- A. In a case of optic neuritis in a young woman with fatigue.
- B. In a case of transverse myelitis in a young woman with CSF oligoclonal bands.
- C. In a case of a 50-year-old woman with paresthesias in her feet and visual symptoms, if the MRI shows more than three white matter lesions none of which enhances after gadolinium.
- D. In a case of 25-year-old patient with an internuclear ophthalmoplegia and an MRI that shows nine periventricular and juxtacortical white matter lesions with and without gadolinium enhancement.
- E. In the case of a young woman with depression, fatigue, and CSF pleocytosis

Answer: D The diagnosis of multiple sclerosis can be made in a patient with a clinically isolated syndrome and no other better explanation only if the MRI fulfills criteria for dissemination in space and time (enhancing and nonenhancing lesions are now interpreted as dissemination in time).

2. A patient with established multiple sclerosis reports urinary frequency and urgency resulting in incontinence twice a month. The best advice is to:
- A. Check a urinalysis for infection, exclude urinary retention by checking a postvoid residual, and consider oxybutynin or other bladder medication to suppress detrusor muscle spasm.
 - B. Check a urinalysis for infection, exclude urinary retention by checking a post-void residual, and consider tamsulosin or similar bladder medication to relax external sphincter muscle spasm.
 - C. Recommend botulinum toxin injections without further invasive testing.
 - D. Recommend that this patient learn how to perform intermittent straight catheterization to empty the bladder.
 - E. Treat for urinary tract infection with antibiotics and then reassess.

Answer: A A urinary tract infection and component of urinary bladder retention first need to be excluded, and then the patient should be considered for treatment with drugs that relax the detrusor muscle contraction that is likely mediating her urgency and incontinence. Botox is a reasonable alternative but only after retention and infection are excluded. Tamsulosin might relieve bladder retention but will not help detrusor muscle spasm.

Ch / 412 **MENINGITIS: BACTERIAL, VIRAL, AND OTHER**

1. A 16-year-old girl develops fever, photophobia, stiff neck, hemorrhagic lesions in the skin, and drop in blood pressure. Symptoms first started 6 hours ago. Appropriate management would be:
- A. Investigate with an MRI brain scan and CSF analysis, and then treat for viral or bacterial meningitis depending on results.
 - B. Maintain blood pressure, then initiate investigations with MRI of brain, blood culture, and CSF analyses.
 - C. Precious time may be lost in obtaining an MRI scan; once blood pressure is maintained, obtain CSF analyses to make diagnosis.
 - D. Obtain blood cultures, treat with intravenous antibiotics, maintain blood pressure, and then initiate investigations

Answer: D The patient most likely has meningococcal meningitis, which is fulminant and can be fatal if not treated immediately. Enteroviruses can cause a skin rash but not hemorrhagic lesions. This clinical presentation is also termed *Waterhouse-Friderichsen syndrome*, and the drop in blood pressure can be due to bleeding in the adrenal glands.

2. A 76-year-old man with neutropenia following treatment for colon cancer develops dysphagia, ataxia, and left-sided weakness. MRI of the brain shows a contrast-enhancing lesion in the brain stem and extending into the cerebellum, with enhancement of the meninges in the posterior fossa. The most likely diagnosis is:
- A. Metastatic colon cancer.
 - B. Metastatic cancer from another primary source such as lung.
 - C. Brain abscess and meningitis due to *Mycobacterium tuberculosis*.
 - D. Viral encephalitis.
 - E. *Listeria* brain abscess and meningitis.

Answer: E Colon cancer rarely goes to the brain. Some metastatic cancers seed the meninges and cause carcinomatous meningitis at the base of the skull; these metastases can result in multiple cranial nerve palsies, but they do not invade the brain stem. Neutropenia predisposes a person to bacterial infections, and *Listeria* commonly invades the brain stem and posterior fossa and can occur in the absence of intestinal symptoms. The term *rhombencephalitis* is often used to describe it. Animal models show that the bacteria can travel from the intestine to the brain stem via the vagus nerve.

3. Point(s) to consider for the use of corticosteroids as an adjunctive therapy for bacterial meningitis is/are:

- A. It should be initiated before or simultaneously with the use of antibiotics.
- B. Its use has been associated with a decrease in morbidity and mortality from bacterial meningitis if used early in the course of the illness.
- C. It acts by decreasing injury that otherwise would be caused by inflammatory mediators.
- D. All of the above.
- E. A and B only.

Answer: D Two landmark studies provide strong evidence in support of the use steroids and an adjunctive treatment for bacterial meningitis.

4. Recurrent aseptic meningitis with history of genital lesions is usually due to:

- A. Herpes simplex virus type 2.
- B. Syphilis.
- C. Behçet disease.
- D. All of the above.

Answer: D Herpes simplex virus type-2 can be diagnosed by PCR on the CSF, syphilis by testing for VDRL in the CSF, and Behçet disease is usually associated with orogenital ulcers and evidence of demyelination on the MRI scan of the brain.

1. A patient with a solitary large ring-enhancing lesion with a necrotic center on magnetic resonance imaging (MRI) should be treated by:

- A. Surgical drainage
- B. Empirical antibiotics
- C. An investigation for peripheral source of infection and treatment with appropriate antibiotics
- D. Steroids and then biopsy of the lesion
- E. Repeated MRI scans with intervention only if the lesion grows further

Answer: A All large lesions will require drainage. Antibiotics cannot penetrate the capsule, and even if they did, there would be a dose gradient with low concentrations of the antibiotic in the center of the lesion. Aggressive tumors rarely have a necrotic center, so some tissue should also be obtained from the edge of the lesion.

2. An HIV-infected immunocompromised patient has multiple ring-enhancing lesions on brain MRI. The appropriate management would be:

- A. Empirical antituberculosis therapy
- B. Brain biopsy to determine if it is a tumor, such as central nervous system lymphoma, or infection followed by biopsy-guided treatment
- C. Empirical antitoxoplasmosis therapy
- D. Cerebrospinal fluid analysis should be performed for detection of microorganisms and for detection of tumor cells by flow cytometry, followed by treatment based on the results.
- E. Positron emission tomography should be performed to see if there are any peripheral lesions that may be easier to biopsy.

Answer: C Multiple ring-enhancing lesions in an HIV-infected patient with a low CD4 cell count are most often due to toxoplasmosis. Owing to immunosuppression, the capsule is not well formed, and the lesions often are not large; as a result, antibiotic penetration is good. If the patient does not respond to treatment in 2 weeks as determined by a repeat MRI scan, brain biopsy should be considered.

3. A 35-year-old man with sinusitis for 2 weeks develops blurry vision with a left-sided frontal headache. Examination shows mild proptosis and conjunctival edema with retinal venous hemorrhages. Appropriate management would be:

- A. Computed tomography (CT) scan of the orbit to localize the infection or abscess in the orbital bone, because it may extend to the orbit by eroding the sinuses
- B. Drain the sinuses to diagnose the organism, and treat immediately with appropriate antibiotics.
- C. Obtain an echocardiogram to exclude infective endocarditis as a source of the infection.
- D. Treat empirically with antibiotics and corticosteroids.
- E. Obtain MRI and MR venogram to look for occlusion of venous sinuses.

Answer: E The clinical presentation is suggestive of a cavernous sinus thrombosis, which may occur because of extension of infection from sinusitis. A combination of antibiotics and anticoagulation may be necessary. The cavernous sinus thrombosis can spread to other sinuses and cause venous infarcts in the brain. Systemic infection may also require emergent treatment.

4. Which of the following is true regarding mycotic aneurysms?

- A. They are caused by mycoses or fungal infections.
- B. They represent metastatic infections in which the microorganisms get lodged in the blood vessels and cause the aneurysm.
- C. As far as possible, all cerebral mycotic aneurysms should be treated with surgical excision or endovascular coils/embolization.
- D. The most common clinical manifestation is when occlusion of the aneurysm leads to either an infarct or abscess.
- E. They can occur in the brain without any systemic infection.

Answer: B Mycotic aneurysms may be due to a variety of different microorganisms. The primary infection is usually in the heart, from where the organism may embolize to the brain or other organs. For example, splinter hemorrhages may be seen in the nail beds, and retinal hemorrhages may be seen owing to occlusion of the distal small blood vessels. The most common manifestation of a mycotic aneurysm is a subarachnoid hemorrhage, which is often fatal. Surgical or endovascular intervention should be considered in a nonruptured aneurysm that is 1 cm or greater in diameter.

5. Over a period of 2 to 3 weeks, a 50-year-old woman developed pain in the right ear, with a low-grade fever followed by headache, nausea, vomiting, loss of hearing, and vertigo. The most likely diagnosis is:

- A. Thrombosis of the lateral venous sinuses
- B. Middle ear infection
- C. Meniere disease
- D. Brain stem abscess
- E. Any of the above

Answer: A Middle ear infections are not associated with vertigo. Meniere disease does not cause earache and fever. Brain stem abscess is unlikely to cause earache or loss of hearing. Hence, the most likely cause of this constellation of symptoms is a lateral venous sinus thrombosis.

1. A 57-year-old man presents with 3 days of fever and headache, which were followed today by lethargy and right hemiparesis. The best test to confirm a suspected diagnosis of herpes simplex encephalitis is:

- A. Computed tomographic (CT) scan of the head
- B. Magnetic resonance imaging (MRI) of the head
- C. electroencephalogram (EEG)
- D. Spinal fluid herpes simplex virus culture
- E. Spinal fluid polymerase chain reaction (PCR) for herpes simplex virus

Answer: E Herpes simplex virus spinal fluid PCR is the most sensitive and specific test to confirm herpes simplex encephalitis (HSE). MRI of the brain frequently will show highly suggestive findings of HSE, but the same findings can be mimicked by autoimmune limbic encephalitis or viral encephalitis associated with HHV-6. CT scanning is usually normal unless there is a hemorrhagic lesion. EEG in HSE shows periodic lateralized epileptiform discharges, but so does infarction of the temporal lobe. Herpes simplex virus culture from spinal fluid is insensitive for making the diagnosis.

2. Empirical treatment to be started at the time of presentation for a patient with suspected herpes simplex encephalitis should include antibiotics (vancomycin and ceftriaxone) and:

- A. Acyclovir
- B. Cidofovir
- C. Dexamethasone
- D. Phenytoin
- E. Mannitol

Answer: A Acyclovir is the treatment of choice for herpes simplex encephalitis, and a successful outcome depends on its early initiation before diagnostic microbiological studies are completed. Cidofovir is principally used for CMV infection. Empirical dexamethasone therapy is principally used in bacterial meningitis. Phenytoin anticonvulsant therapy is generally not routinely recommended for encephalitis unless clinical seizures are manifest. Mannitol is not indicated in early herpes simplex encephalitis.

3. A 48-year-old man presents with low-grade fever, malaise, and a change in mental status 3 weeks after a bite by a bat. Other clinical features that would support a clinical diagnosis of rabies encephalitis include all of the following **except**:

- A. Laryngospasm when trying to drink water
- B. Meningismus with neck flexion
- C. Ascending paresthesias in the upper limb on which he was bitten
- D. Flaccid paralysis of all four limbs
- E. An agitated mental state

Answer: B Meningismus is only rarely associated with rabies meningoencephalitis. Laryngospasm in response to oral fluids (hydrophobia) is characteristic of rabies encephalitis because of brain stem involvement with disinhibition of bulbar reflexes. Paresthesias in the bitten limb are common owing to sensory nerve involvement and axonal transport of the virus. One form of rabies involves the spinal cord and anterior horn cell and causes acute flaccid paralysis, which sometimes mimics Guillain-Barré syndrome. Rabies encephalitis can cause either agitation or a depressed level of consciousness.

1. A 65-year-old man from the U.S. state of Kansas develops a rapidly progressive dementia and undergoes a brain biopsy. He is found to have Creutzfeldt-Jakob disease. He is a rancher and is a fan of steak tartare (raw beef), which he has eaten several times each month for many decades. There is no family history of dementia. In order of probability, the most likely cause of his disease is:

- A. Sporadic, genetic, dietary exposure
- B. Dietary exposure, sporadic, genetic
- C. Genetic, dietary exposure, sporadic
- D. Sporadic, dietary exposure, genetic
- E. *Mycobacterium bovis*, dietary exposure, sporadic

Answer: A Sporadic, genetic, dietary exposure. Virtually all cases of Creutzfeldt-Jakob disease are either sporadic (90%) or genetic (10%). Consumption of beef can cause CJD if the beef is contaminated with prions, but epidemic bovine spongiform encephalopathy (BSE) has not occurred in the United States. Interestingly, it appears that very rare sporadic cases of BSE do occur in U.S. cattle, but it is highly unlikely that the described patient would have acquired CJD through his diet for the following reasons: (1) In the BSE/ vCJD epidemic in Great Britain, there was only about 1 human vCJD case per 1000 diagnosed BSE cases in cattle; (2) the rate of sporadic BSE in cattle is probably on the order of 1 per million or less; (3) consumption of raw beef is not a particularly risky behavior with regard to prion disease, because cooking does not significantly inactivate prions if they are present in meat. *M. bovis* can cause an encephalitis, but the histopathologic diagnosis of prion disease is highly specific, so a misdiagnosis on brain biopsy would not be likely.

2. A 45-year-old man develops progressive confusion and gait ataxia over a period of 8 weeks. He was previously entirely well and has no history of substance abuse. On examination, he is alert but oriented only to name and year. He scores 10/30 on the Folstein mini-mental status exam. There is myoclonus of the limbs, diffuse hyperreflexia, and an unstable gait. Cerebrospinal fluid (CSF) is abnormal with a protein of 85 mg/mL. An assay for the 14-3-3 protein in CSF is positive. Which of the following further diagnostic tests would be most appropriate to obtain next?

- A. Brain biopsy
- B. Levels of serum antibodies against thyroid peroxidase and thyroglobulin
- C. An electroencephalogram (EEG)
- D. Positron emission tomography (PET) of the brain using fluorodeoxyglucose

Answer: B The patient presents with a rapidly progressive dementia. All the tests listed might have some role in the evaluation of such a patient, but the best approach is to look for treatable causes of the condition. Hashimoto encephalopathy is an autoimmune condition associated with high levels of serum antibodies to thyroglobulin or thyroid peroxidase antigens. Importantly, it can mimic several features of CJD, including causing myoclonus, elevated levels of 14-3-3 protein in the CSF, and periodic sharp waves on the EEG. Brain biopsy should be considered, but the procedure is relatively morbid and a specific diagnosis is not often obtained, so it would not usually be the next test performed. PET scan is not particularly useful in the evaluation of most cases of rapidly progressive dementia.

3. A 50-year-old woman develops signs of depression, followed 2 months later by memory problems. Her family history is notable for her father dying at age 60 of a rapidly progressive dementia that was found at autopsy to be Creutzfeldt-Jakob disease. Her paternal grandfather also died of a rapidly progressive dementia at age 43. On examination, she appears anxious and depressed. She has modest cognitive impairment, scoring 25/30 on the mini-mental status examination. The remainder of her neurologic exam is normal. Which of the following diagnostic approaches would be most appropriate?

- A. Magnetic resonance imaging (MRI) of the brain, looking for increased FLAIR signal in the thalamus
- B. EEG

- C. Neuropsychiatric testing
- D. Genetic testing to determine the sequence of the *PRNP* open reading frame
- E. A lumbar puncture, with CSF assays for cell count, protein, glucose, and 14-3-3 levels

Answer: D All of the listed tests might be useful in the evaluation of this patient. However, the family history strongly points to inherited prion disease. Because the patient's father was affected, she has a 50% chance of carrying a mutation in *PRNP* and a high likelihood (generally 90% or greater) of developing disease if she carries a mutation. Her clinical findings are consistent with the initial manifestations of prion disease, although other diagnoses, such as depression and pseudodementia, should be considered. Finding a *PRNP* mutation greatly increases the likelihood that she has early prion disease, whereas negative testing almost excludes this possibility. (Outside of cases cannibalism with Kuru, prion disease is never transmitted infectiously in families). MRI, EEG, or CSF 14-3-3 testing are neither sufficiently sensitive nor specific to diagnose or exclude prion disease, and the sensitivity of these tests is particularly poor in genetic cases.

4. Which of the following increase the risk of developing prion disease?
- A. Receiving a blood transfusion from a donor who developed variant CJD 1 year after donating
 - B. Being treated with growth hormone between 1995 and 1998
 - C. Eating sheep eyes
 - D. Caring for a hospitalized patient with Creutzfeldt-Jakob disease
 - E. Receiving a blood transfusion from a donor who developed sporadic CJD 1 year after donating

Answer: A Blood transfusions have been reported to transmit variant CJD, the form of human prion disease caused by eating meat from cattle infected with BSE prions, to three recipients. In contrast, there is no evidence the more common sporadic form of prion disease can be transmitted by blood or blood products. Growth hormone derived from cadaveric human pituitary is implicated in more than 200 cases of CJD in recipients, but the recombinant form of the protein that has been used since the late 1980s has never transmitted prion disease. It used to be thought that the high rate of CJD among a group of Jews originating from Libya was caused by eating sheep eyes, but it is now known that a genetic form of prion disease caused by a mutation changing glutamate to lysine at codon 200 of *PRNP* is prevalent in this population. There is no evidence for the transmission of prion disease from patients to health care providers.

1. A 12-year-old Muslim boy participated in the observance of Ramadan for the first time. After 10 days of daytime fasting, during which he frequently ended his fast by consuming candy, he began vomiting. Three days later he complained of blurred and double vision and trouble walking. He gradually became lethargic and disoriented. On examination, he was apathetic, had lateral rectus palsy, and nystagmus in horizontal gaze, and he had a broad-based gait with inability to tandem walk. Dysmetria was present in the legs but not the arms. Computed tomography and cerebrospinal fluid examinations were normal. Intravenous (IV) hydration did not improve his oculomotor findings, which resolved with IV thiamine. His mental status changes improved after 2 weeks. The diagnosis is:
- A. Dehydration
 - B. Copper deficiency
 - C. B1 (thiamine) deficiency
 - D. Meningococcal meningitis
 - E. Pellagra

Answer: C Thiamine (B1) deficiency can cause Wernicke encephalopathy even in children, especially when glucose is consumed without preceding thiamine. Thiamine supplies last about 2 to 3 weeks in normal states, less in situations requiring high energy. B12 deficiency occurs in vegans and older

patients with pernicious anemia, but a period of at least 12 months is required to deplete B12 stores. Copper deficiency resembles B12 clinically and similarly takes several months to develop, especially after gastric bypass surgery. Meningococcal meningitis was a problem in pilgrimages to Mecca, but now a vaccine must be demonstrated by the Saudi government prior to entering the country.

2. A 40-year-old woman presents with very profound proximal weakness and areflexia 8 weeks after “lap band” bariatric surgery, with which her stomach size was severely restricted. Since the operation, she has suffered from unremitting vomiting and has consumed only liquids, with no vitamin supplements. Quadriceps biopsy shows necrosis and fat replacement of muscle. The diagnosis is:

- A. Alcoholic proximal myopathy
- B. Magnesium deficiency
- C. Vitamin D deficiency
- D. Carnitine deficiency
- E. Thiamine deficiency

Answer: E Thiamine deficiency is most often found in patients who have excessive recurrent vomiting, and is famously associated with Wernicke encephalopathy followed by Korsakoff syndrome, or peripheral neuropathy (beri-beri). Alcohol use and vitamin D deficiency cause a milder myopathy, and carnitine is associated with central nervous system dysfunction.

3. A 35-year-old Indian woman in her fifth pregnancy presents with leg weakness and spasticity, pain in her feet, and fear of delivering a baby with deformities as she had in her last pregnancy. She has used prenatal vitamins and extra folate because she knew that her vegetarian diet may be lacking some nutrients. Her deficiency is due to:

- A. Folate
- B. Thiamine
- C. B12
- D. Iron
- E. B6

Answer: C B12 is present in meat and some nuts, but prolonged reliance on a vegetarian diet (>18 months) can use up all stores from the liver, especially in the face of multiple pregnancies. B12 deficiency, like folate deficiency, is associated with an increased risk of neural tube defects. Clinically it causes a combined spinal cord degeneration of posterior columns, which leads to proprioception deficits, and lateral columns, which leads to spasticity. It also is frequently accompanied by a peripheral neuropathy that may be painful. Although up to 25% of Indian women are folate deficient, it is correctable with vitamin supplements, which she is using. Other deficiencies produce anemia, neuropathy, and mental status changes but not myelopathy.

4. A famine relief agency flies to Nigeria in the face of a drought that has compromised the already marginal nutritional status of the residents, who rely almost exclusively on flour from the cassava plant for their food. Because there is limited water, the tuber is not always detoxified. The population has many older men who have trouble walking because of a spastic gait and inability to locate their feet. Some are blind or deaf as well. Some women and children with more severe permanent weakness and spasticity cannot walk at all. The cause is:

- A. Niacin deficiency
- B. Lead poisoning from contaminated well water
- C. B1 deficiency with pellagra
- D. Lathyrism
- E. Cassavism

Answer: E Cassavism is caused by a failure to remove toxins from the cassava plant and causes variable syndromes depending on patients’ age and probable simultaneous vitamin deficiencies. Niacin

deficiency causes peripheral neuropathy but not spasticity. Lead poisoning can cause isolated nerve palsies, especially the radial nerve, and static encephalopathy in children but not spasticity. Thiamine deficiency can cause peripheral neuropathy but with no spinal cord involvement. Lathyrism causes spasticity but is caused by reliance on chick peas as a single food source.

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CONGENITAL, DEVELOPMENTAL, AND NEURO CUTANEOUS DISORDERS

1. An 18-year-old man with more than 10 café au lait spots, axillary freckling, and a family history of neurofibromatosis type 1 has recently come into your practice for primary care. He is otherwise normal. Which of the following should be done as part of routine surveillance for complications of neurofibromatosis type 1?

- A. Annual brain MRI scan
- B. Annual physical examination with blood pressure
- C. Annual electrocardiogram
- D. Annual orthopedic evaluation
- E. Annual ophthalmologic examination

Answer: B Current guidelines recommend annual physical examination and blood pressure check in adults with neurofibromatosis type 1. Other evaluations should be based on presence of symptoms or history of nervous system, skeletal or cardiovascular abnormalities. This patient has only cutaneous manifestations.

2. A 21-year-old with tuberous sclerosis has been diagnosed recently with a subependymal giant cell astrocytoma. Which of the following treatments should be considered to reduce the growth of this tumor?

- A. Everolimus
- B. Bevacizumab
- C. Rituximab
- D. Cyclophosphamide
- E. Ventriculoperitoneal shunting

Answer: A Everolimus has been shown in a controlled phase 3 randomized trial to reduce the size of subependymal giant cell astrocytomas by more than 50% in 35% of study participants. Bevacizumab has been used in patients with neurofibromatosis type 2 and vestibular schwannomas to improve hearing. The other treatments have not been shown to reduce the growth of subependymal giant cell astrocytomas.

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AUTONOMIC DISORDERS AND THEIR MANAGEMENT

1. A 38-year-old woman seeks evaluation for impaired concentration, severe insomnia, excessive sweating, fluctuating blood pressure, and painful muscle cramps. Polysomnography shows complete absence of sleep during the recording. Electromyography shows hyperexcitability of peripheral nerves. Computed tomography of the chest shows an anterior mediastinal mass. Autoantibodies to which of the following receptors are most likely to be found in this patient?

- A. Nicotinic ganglionic acetylcholine receptor
- B. Nicotinic acetylcholine receptor
- C. Voltage-gated sodium channel
- D. Voltage-gated calcium channel
- E. Voltage-gated potassium channel

Answer: E This patient has typical clinical features of Morvan syndrome, which is an autoimmune disorder characterized by central, autonomic, and peripheral nerve hyperactivity. As many as 50% of cases have a thymoma. The characteristic antibody is to the voltage-gated potassium channel. By contrast, antibodies to the voltage-gated calcium channel are associated with Lambert-Eaton myasthenic syndrome. Antibodies to the nicotinic acetylcholine receptor are associated with myasthenia gravis, and antibodies to the ganglionic receptor are associated with autoimmune autonomic ganglionopathy. Antibodies to voltage-gated sodium channels are associated (depending on the specific protein) with epilepsy, hyperkalemic periodic paralysis, paramyotonia congenita, long QT syndrome, Brugada syndrome, and idiopathic ventricular fibrillation.

2. A 48-year-old previously healthy man taking no medications presents with a 1-year history of progressive fatigue following exercise, dizziness when showering, and inability to sustain an erection. His blood pressure is 136/68 mm Hg supine, 130/62 mm Hg seated, and 90/54 mm Hg standing, and his heart rate is 70 beats per minute in all positions. Which of the following laboratory tests would be useful in evaluating this patient's adrenergic failure?

- A. Plasma level of free metanephrine
- B. Blood pressure response to carotid sinus massage
- C. Heart rate response to periodic deep breathing
- D. Blood pressure response to forced expiration
- E. Heart rate response to forced expiration

Answer: D This patient has orthostatic hypotension, which is likely neurogenic because it is severe and without a compensatory tachycardia. Patients with autonomic failure experience orthostatic hypotension because the sympathetic nervous system is unable to increase peripheral vascular resistance, which is regulated by postganglionic adrenergic neurons, in response to the downward pooling of venous blood when standing. In addition to upright tilt table testing, blood pressure recovery and overshoot in response to the Valsalva maneuver (which consists of forced expiration of 40 mm Hg for 15 seconds) is useful in evaluating and quantifying adrenergic function. The heart rate response to the Valsalva maneuver and to periodic deep breathing assess cardiovagal rather than adrenergic function. Carotid sinus massage may be useful, not in assessing the integrity of adrenergic function but rather in evaluating reflex syncope with bradycardia. Plasma (or urine) free metanephrine levels are useful in detecting pheochromocytoma, which is a neuroendocrine tumor of the adrenal medulla.

3. A 62-year-old man with a 10-year history of diabetes mellitus has recently developed lightheadedness upon standing when he gets out of bed each morning. He has not had vertiginous sensations of motion or rotation. His only medication is metformin. Glucose by fingerstick during symptoms was 166 mg/dL. Neurologic examination finds absent Achilles tendon reflexes and decreased sensation to pinprick below the mid-calves. Blood pressure measured supine is 170/88 mm Hg, with heart rate 74 beats per minute. After 2 minutes of standing, blood pressure is 132/72 mm Hg without symptoms, and heart rate is 76 beats per minute. Which of the following treatment recommendations is most appropriate?

- A. β -Blocker metoprolol 50 mg twice daily
- B. Tamsulosin 0.4 mg each morning
- C. Meclizine
- D. A glass of orange juice, 8 oz. each morning
- E. Bolus water drinking, 16 oz. each morning

Answer: E This patient's postural lightheadedness is most probably caused by orthostatic hypotension, which is defined as a reduction in systolic blood pressure of at least 20 mm Hg or a reduction in diastolic blood pressure of at least 10 mm Hg, with or without symptoms, within 1 to 3 minutes of assuming a standing posture. Symptoms such as lightheadedness can be variably present. In this case, the most likely cause of orthostatic hypotension is an autonomic neuropathy, because signs of

sensory and motor peripheral neuropathy are also present. An established treatment for orthostatic hypotension is bolus water drinking, which induces an osmopressor reflex mediated through the sympathetic nervous system. Water drinking is effective only if it is hypo-osmotic (unlike fruit juices which are hyperosmotic). Although micturition presyncope might be a consideration in this patient if his symptoms were to occur while voiding and if his prostate were enlarged, tamsulosin, which is an α -adrenergic antagonist used to treat benign prostatic hyperplasia can worsen orthostatic hypotension. β -Blockers, which are useful in treating hypertension, can also worsen orthostatic hypotension. The antihistamine meclizine can be useful in treating benign paroxysmal positional vertigo, which is a different form of dizziness characterized by a rotational sensation following head movement and is typically not associated with orthostatic hypotension.

4. A 27-year-old man who is paraplegic following traumatic injury to his spine at the level of T2 complains of recurrent headaches. The headaches occur nearly daily, persist for 30 to 60 minutes, and are accompanied by facial sweating, flushing, and elevations in blood pressure as high as 180/110 mm Hg, but no visual symptoms. The patient rates the intensity of the headaches as 9 on a scale of 0 to 10. Ibuprofen and hydrocodone have provided no relief. Computed tomography of the brain is normal. Which of the following is the most appropriate recommendation?

- A. Suprapubic ultrasound to assess for a full bladder
- B. Begin hydrochlorothiazide to treat hypertension
- C. Begin midodrine to treat orthostatic hypotension
- D. Urine 5-hydroxyindoleacetic acid to screen for carcinoid
- E. Urine metanephrine to screen for pheochromocytoma

Answer: A This patient has autonomic dysreflexia, which is a paroxysmal disorder of excessive sympathetic outflow. Autonomic dysreflexia, which can follow spinal cord injuries above the level of T5, is triggered by any strong visceral or peripheral sensory stimulus, which the patient may or may not be able to perceive. The most appropriate treatment is identification and resolution of the sensory stimulus, such as a distended bladder, distended bowel, or skin irritation. Pharmacologic treatment of the hypertension without removing its source would be unlikely to succeed and could cause hypotension in between hypertensive episodes. Midodrine, which is useful in treating orthostatic hypotension, can worsen, not alleviate, hypertension. Pheochromocytoma also produces paroxysmal sympathetic surges but is quite rare, whereas autonomic dysreflexia is common in patients with spinal cord injury. Carcinoid syndrome also produces flushing, typically with diarrhea, but not hypertension.

5. A 42-year-old premenopausal woman reports frequent, diffuse, and embarrassing excessive sweating involving her face, neck, chest, and back. The sweating occurs not only in response to exercise and in hot weather but also at rest and in cool environments. Her medications are timolol eye drops for glaucoma, bupropion for anxiety, and oxycodone for chronic low back pain. Her blood glucose level, thyroid function, and complete blood count are normal. Which of the following is the most appropriate treatment recommendation for the patient's complaint?

- A. Oral anticholinergic agent
- B. Change or eliminate current medications
- C. Replace fluid lost by drinking more water
- D. Botulinum toxin subcutaneous injections
- E. Tap water iontophoresis

Answer: B This patient has either essential hyperhidrosis or drug-induced hyperhidrosis or both. As the known side effects of two of her current medications—the serotonin reuptake inhibitor bupropion and the opioid oxycodone—include increased sweating, reassessment of the need for continuation of those medications or consideration of switching to alternative agents would be the most direct approach to resolving her hyperhidrosis. Although an oral anticholinergic agent could be used to reduce sweating (acetylcholine is the neurotransmitter at the eccrine neuroeffector junction),

anticholinergic agents are contraindicated in glaucoma because they increase intraocular pressure. Drinking more water, while appropriate to replace fluid lost if the sweating is profuse or frequent, would not improve the patient's symptom. Botulinum toxin injections and tap water iontophoresis are appropriate treatments for some regional forms of hyperhidrosis, but they are not indicated for generalized hyperhidrosis; it would be impracticable to treat such a wide area of skin.

Ch / 419 **AMYOTROPHIC LATERAL SCLEROSIS AND OTHER MOTOR NEURON DISEASES**

1. A 53-year-old woman presents with a 12-month history of progressive wasting and weakness of the right hand. She had been aware of muscle cramps and muscle twitching affecting the proximal upper limb muscles. In the preceding 3 months, she had developed mild slurring of speech. Neurologic examination revealed a combination of upper and lower motor neuron signs affecting the bulbar and upper limb regions. Neurophysiologic examination revealed normal nerve conduction but evidence of active denervation in the bulbar, upper limb, and lower limb territories, as well as the thoracic paraspinal muscle. A diagnosis of upper limb onset amyotrophic lateral sclerosis was made. Which of the following additional clinical features may be present?

- A. Emotional lability
- B. Distal sensory loss in the limbs
- C. Restriction of conjugate eye movements
- D. Urinary incontinence
- E. Pain in the right arm

Answer: A Emotional lability is commonly present in amyotrophic lateral sclerosis (ALS), especially in patients with upper motor neuron and bulbar signs. Sensory loss and pain are not expected to be present in patients with ALS and should be considered “red flags” to prompt consideration of alternative diagnoses. Pain may arise later in the disease course (e.g., development of a frozen shoulder secondary to immobility). Abnormalities of eye movements and pelvic floor muscles are rarely seen in patients with ALS, because the motor neurons within the cranial nerve motor nuclei (controlling eye movements) and Onuf nucleus in the sacral spinal cord are less vulnerable to the disease process compared to other groups of motor neurons.

2. A 62-year-old man presented with a 6-month history of progressive lower limb weakness, starting initially with right-sided footdrop. There was a family history of neurologic disease in that his older brother had died from ALS 5 years earlier after a 2-year disease course. The patient's mother had developed dementia at the age of 58, and the family had observed a marked personality change and behavioral disturbances during the 4-year disease course. Neurologic examination and testing were consistent with the diagnosis of ALS. Genetic testing showed the presence of a pathologic hexanucleotide expansion in intron 1 of the *C9ORF72* gene. Which of the following statements are correct?

- A. The pathologic changes in the central nervous system of this patient are likely to be identical to those present in most cases of sporadic ALS.
- B. The patient's condition is likely to be linked to the dementia disorder that developed in his mother.
- C. The pattern of inheritance of this disorder is likely to be autosomal recessive.
- D. Riluzole is not effective as a disease-modifying therapy in this subtype of ALS.
- E. *C9ORF72* mutations are a less common cause of ALS than *SOD1* mutations.

Answer: B *C9ORF72*-related ALS is an autosomal dominant disorder (with incomplete penetrance). This gene change can also cause frontotemporal dementia, the features of which were present in the patient's mother. Patients with *C9ORF72*-related ALS are more likely to develop cognitive disturbance and have a family history of dementia or psychosis. It is unknown whether riluzole has a disease modifying effect in this subgroup of patients. The pathology of *C9ORF*-related ALS is characteristic,

with protein inclusions that stain for P62, but which are negative for TDP-43 in neurons outside the motor system (e.g., cerebellum, hippocampus).

3. A 47-year-old man was diagnosed with lower limb-onset ALS 2 years ago. He now reports that he has not been sleeping well in the previous 2 months and that he has experienced loss of appetite and weight loss, though his speech and swallowing function remained normal. In the preceding 2 weeks, he noticed that he was tending to wake up with a bifrontal morning headache that would resolve approximately 30 minutes after getting out of bed. Respiratory assessment showed that his forced vital capacity (FVC) was 70% of predicted for his age and height. Which of the following management plans would be most appropriate?

- A. Advise the patient to lie flat in bed at night, using only one pillow.
- B. Gastrostomy tube insertion because of the weight loss
- C. Nighttime sedation to improve the quality of sleep
- D. Overnight oximetry followed by a trial of noninvasive ventilation
- E. Administration of analgesia for the morning headaches and referral for repeat brain imaging to exclude the presence of an intracranial space-occupying lesion

Answer: D This patient has classic symptoms of neuromuscular respiratory failure. Initially the weakness of the respiratory muscles tends to cause problems during the night, when REM sleep may further compromise the function of weak respiratory muscles and the lying position may impair the function of a weak diaphragm. Intermittent hypoxia causes nocturnal restlessness and interruption of sleep, and CO₂ retention causes loss of appetite and morning headaches. Diaphragmatic weakness is *more* symptomatic when the patient attempts to lie flat, causing orthopnea. The patient should be advised to sleep in a more upright position. Overnight oximetry will be helpful in confirming the presence of nocturnal derangement of the blood gases. Nighttime sedation should *not* be used, because it may cause suppression of the respiratory drive and further compromise of respiratory function. If the presence of abnormal blood gases is confirmed, the patient may well benefit from the use of noninvasive ventilation, both in terms of quality of life and life expectancy. Gastrostomy tube insertion can be a helpful symptomatic measure in the presence of dysphagia but would not normally be considered for anorexia in the absence of difficulty with swallowing.

4. A 40-year-old man presents with a 2-year history of tremor of his hands, as well as muscle twitching, cramps, and slowly progressive weakness of the lower limb muscles. He also has mild slurring of his speech. Clinical examination reveals perioral and thigh muscle fasciculation and symmetrical proximal lower limb weakness with normal muscle tone and reflexes and flexor plantar responses. He also has mild distal sensory loss to light touch and pinprick in the lower limbs and a degree of gynecomastia. The neurophysiologic assessment shows evidence of neurogenic changes, predominantly in the lower limb and tongue muscles. Which additional investigation is likely to prove most useful in establishing the diagnosis in this patient?

- A. Muscle biopsy
- B. Genetic analysis of the *C9ORF72* gene
- C. MRI of the lumbosacral spine
- D. Cerebrospinal fluid examination
- E. Genetic analysis of the androgen receptor gene

Answer: E This male patient had evidence of a pure lower motor neuron disorder that predominantly involved the lower limb and bulbar muscles at the time of presentation. The clinical clues (or red flags) that Kennedy disease might be the correct diagnosis include: the relatively indolent course of disease progression, the presence of distal sensory loss in the lower limbs that would not be commonly found in other motor neuron disorders such as ALS, and the presence of gynecomastia (a manifestation of androgen insensitivity). The diagnosis is established by detecting the presence of a CAG expansion of more than 40 repeats in the first exon of the androgen receptor gene located on chromosome Xq11-12.

1. A 54-year-old man has been recently diagnosed with anti-AChR-positive myasthenia gravis. The disease has had an acute onset and rapid progression, leading in few weeks to severe generalized weakness with marked bulbar symptoms, including dysphagia, dysarthria, neck weakness, and impaired respiratory function. A thymoma is detected on thoracic computed tomography scan. Symptoms are not satisfactorily relieved by full-dose pyridostigmine treatment. Which of the following should be considered as first therapeutic option in this case?
- A. Immediate thymectomy
 - B. Plasmapheresis (or immunoglobulin infusion) and prednisone
 - C. Plasmapheresis
 - D. Azathioprine
 - E. Rituximab

Answer: B Thymectomy is indicated and should be performed as soon as possible because of the presence of a thymoma. The patient has severe and poorly controlled symptoms. In this situation, surgery should be deferred until the myasthenia gravis improves. Plasmapheresis (or immunoglobulin infusion) provides a rapid onset of improvement, which is, however, short-lived unless immunosuppressive treatment is added. Prednisone is the first-choice immunosuppressant because of its short-latency effect; the association of plasmapheresis (or immunoglobulin infusion) can enhance the therapeutic effect and minimize the temporary exacerbation that can occur at the start of prednisone administration. Because of its long-latency effect, azathioprine is not the first option in this case. Rituximab is reserved for refractory disease.

2. A 70-year-old woman presents with asymmetrical ptosis, which is more pronounced on her right eye, and intermittent diplopia. Her symptoms fluctuate daily, and they improve with rest but worsen in the evening. Her symptoms have been present for more than 1 year, with periods of spontaneous remission. On the whole, the symptoms do not interfere with her daily activities. On clinical examination, mild fatigability of neck extensors and arm proximal muscles is also evident. Myasthenia gravis is diagnosed by detecting anti-AChR antibodies, increased jitter on SF-EMG, and a positive response to neostigmine. Thoracic computed tomography scan is negative. The patient also has diabetes controlled by diet. Which of the following is the correct recommendation as first treatment in this patient?
- A. Pyridostigmine
 - B. Prednisone and azathioprine
 - C. Thymectomy
 - D. Plasmapheresis
 - E. Fluoxetine

Answer: A This patient has mild generalized myasthenia gravis with predominantly ocular symptoms. The disease has a slow course and is not disabling. In this context, treatment with pyridostigmine can be sufficient to control patient's symptoms and should be tried first. Immunosuppressive therapy (prednisone and azathioprine) and plasmapheresis should be considered if the disease worsens. Thymectomy is not indicated because the patient has late-onset nonthymomatous disease. Fluoxetine blocks AChR channels; it is contraindicated in myasthenia gravis, and its use is limited to the treatment of the slow-channel myasthenic syndrome.

1. A 45-year-old woman is having difficulty with near vision tasks in both eyes. What is the likely cause of this problem?

- A. A decreased range of accommodation
- B. Increased opacification of the crystalline lens
- C. A separation of the retina from the retinal pigment epithelium
- D. Scarring on the internal surface of the retina
- E. Neovascularization and scarring of the external retina.

Answer: A At age 45 years, the amount of available accommodative reserve decreases to the point at which reading and other near tasks become difficult. Although cataracts can occur at age 45 years, the incidence is very low, and such early cataracts are usually unilateral. A serous detachment of the retina usually occurs in one eye and causes acquired asymmetrical vision. Scarring of the internal surface of the retina (epiretinal membrane formation) is also usually a unilateral abnormality. Neovascularization of the external surface of the retina (subretinal neovascularization) is also usually a unilateral acquired abnormality.

2. A 35-year-old man developed mild focal upper eyelid pain and swelling associated with a tender mass. What is the likely cause of the mass?

- A. An abscess of the eyelash follicle
- B. A rupture of a meibomian gland
- C. Proliferation of the basal layers of the eyelid epidermis
- D. A blockage of an eccrine duct of the eyelid
- E. Proliferation of non-nodal lymphoid tissue of the conjunctiva.

Answer: B Unilateral eyelid pain and swelling is the usual presentation of a chalazion (rupture of a meibomian gland). A sty, which is an abscess of a pilosebaceous unit, presents with extreme pain and the risk for anterior or posterior cellulites. Basal cell carcinoma is a painless mass. Blockage of an eccrine duct (ductal cyst) is also painless and usually occurs in the conjunctiva. Proliferation of non-nodal lymphoid tissue (lymphoma) is also painless and usually found in the upper or lower fornix of the conjunctiva.

3. A 43-year-old near-sighted man notes the sensation of flashing lights and an increased number of small floaters in the right eye. This afternoon during his annual physical examination, he notes loss of the inferior visual field of that eye. What is the most appropriate course of action?

- A. Chest imaging for a primary neoplasm
- B. Carotid artery imaging
- C. Evaluation for systemic hypertension
- D. Immediate referral for intraocular evaluation
- E. Schedule for next available eye examination

Answer: D Recent onset of the sensation of floaters and flashing lights is the common presentation of retinal detachment. Visual outcome is dependent on early diagnosis and treatment. The other systemic conditions present much differently.

4. A 71-year-old man has noted halos around oncoming car headlights and double vision in only one eye. What is the most likely cause of his vision change?

- A. Intimal thickening of the ipsilateral carotid artery
- B. Cerebral aneurysm
- C. Brain stem vascular insufficiency
- D. Serous retinal detachment
- E. Increase of refractive index of the lens

Answer: E Monocular diplopia (diplopia with one eye open) is a common presentation of a cataract, although corneal surface abnormalities may present similarly. The other conditions present with bilateral diplopia (diplopia disappears with closure of one eye).

5. The notation in a drug insert states that the drug should not be used if the patient has glaucoma. Which type of glaucoma puts the patient at risk for vision loss with this drug?

- A. Chronic open-angle glaucoma
- B. Exfoliative glaucoma
- C. Narrow angle glaucoma
- D. Neovascular glaucoma
- E. Trauma-associated glaucoma

Answer: C The most common cause of nonsteroidal-induced glaucoma is that associated with narrow angle anterior chamber configuration. The other types of glaucoma are not risk factors for drug-induced glaucoma.

6. A 50-year-old man with a hemoglobin A1c level of 10% has noted over the past week that he can read comfortably without his bifocals. What is the significance of this observation?

- A. Induced myopia due to hyperglycemia
- B. Macular edema
- C. Occlusion of a branch retinal artery
- D. Late-stage background diabetic retinopathy
- E. Early-stage proliferative diabetic retinopathy

Answer: A This person has uncontrolled diabetes associated with induced myopia. The induced myopia has corrected his near vision but made his distance vision difficult. All of the other conditions will decrease visual acuity at near.

Ch / 424 **NEURO-OPHTHALMOLOGY**

1. Lesions in which of the following structures could not produce a hemianoptic field defect?

- A. Parietal lobe
- B. Occipital lobe
- C. Temporal lobe
- D. Geniculate ganglion
- E. All of the above

Answer: E Lesions in all of these structures can involve the optic radiations and produce a hemianoptic defect.

2. Which of the following would be atypical for retrobulbar neuritis?

- A. Loss of visual acuity
- B. Swelling of the optic disc
- C. Atrophy of the optic disc
- D. Color saturation
- E. Later development of multiple sclerosis

Answer: B The optic disc looks normal with acute retrobulbar neuritis, but the disc can later become pale and atrophic. Monocular loss of visual acuity and color saturation are common, and more than 50% of patients will eventually be diagnosed as having multiple sclerosis.

3. Which of the following would be atypical for papilledema?

- A. Enlargement of the blind spot
- B. Loss of visual acuity
- C. Gradual loss of peripheral vision
- D. Brief episodes of amaurosis
- E. None of the above

Answer: B Visual acuity is nearly always maintained with papilledema. A, C, and D all occur with papilledema.

4. Which of the following is not associated with Horner's syndrome?

- A. Lateral medullary infarction
- B. Lung cancer
- C. Carotid artery dissection
- D. Anterior communication artery aneurism
- E. None of the above

Answer: D Anterior communicating artery aneurysms can cause an enlarged pupil by compressing the parasympathetic innervation of the pupil, which is carried in the third nerve. The other three conditions all can damage the sympathetic innervation of the pupil, thereby causing Horner's syndrome.

5. A 35-year-old woman with known multiple sclerosis presents with new-onset double vision. Which of the following findings would be unlikely on neurologic examination?

- A. Nystagmus of the abducting eye on lateral gaze
- B. Impaired adduction on lateral gaze
- C. Atrophy of the left optic disc
- D. Enlarged pupil on the left side
- E. Loss of visual acuity on the left side

Answer: D A and B are features of internuclear ophthalmoplegia, which is a common cause of double vision in a patient with multiple sclerosis. Unilateral optic neuritis with visual loss and development of optic atrophy would be common additional findings in patients with known multiple sclerosis. The pupils are symmetrical in patients with optic neuritis because the light reflex is bilateral. Involvement of the parasympathetic control of the pupil would be unusual with multiple sclerosis.

1. A new 62-year-old female patient complains of various bilateral joint pains. In the course of examination, you observe symmetrical parotid gland enlargement, which is soft and nontender to palpation. Intraoral examination is within normal limits. Which of the following is the most appropriate recommendation?

- A. Request labial salivary gland biopsy to evaluate possible Sjögren's syndrome.
- B. Request parotid gland biopsy to exclude multifocal neoplasia, such as lymphoma.
- C. Request a chest radiograph to evaluate possible sarcoidosis.
- D. Request serum anti-SS-A/-B, rheumatoid factor and antinuclear antibody to seek serologic evidence of Sjögren's syndrome.
- E. Request a blood glucose level to consider diabetes.

Answer: E This patient has sialadenosis, distinguished by its bilaterally symmetrical enlargement and the absence of induration, which would indicate an absence of intraglandular inflammation or neoplasia. This condition is most commonly associated with diabetes mellitus or alcoholic cirrhosis,

but it may also occur in patients with gonadal hypofunction, acromegly, chronic pancreatitis, hyperlipoproteinemia, or anorexia nervosa-bulimia. This type of parotid enlargement is self-limited and does not require treatment. Biopsy, which in this condition would show only parenchymal hyperplasia, is not indicated.

2. A 35-year-old female patient who is taking prescription drugs to manage depression complains of a progressive burning sensation on her tongue during the last several months. She smokes one pack of cigarettes per day. On physical examination, the dorsal surface of her tongue exhibits diffuse erythema and generalized atrophy of the filiform papillae. Her oral mucosa is moist, but little saliva accumulates in the floor of her mouth during your examination. Which of the following is the most appropriate recommendation?

- A. Request biopsy of the affected area of her tongue to exclude mucosal dysplasia or neoplasia.
- B. Change her current combination of medications.
- C. Prescribe a course of topical steroid application to reduce the mucosal inflammation.
- D. Prescribe a course of fluconazole, lasting at least 2 weeks or until the erythema resolves and filiform papillae return.
- E. Recommend that she stop smoking.

Answer: D Although smoking cessation is certainly to be recommended for any patient, this patient's lingual mucosal changes are characteristic of mucosal candidiasis, possibly as a result of decreased salivary function from medications used to manage her depression. In patients with little or no residual salivary function (e.g., in advanced Sjögren's syndrome or after head and neck radiation therapy), treatment of oral mucosal candidiasis may require the use of topical antifungal therapy.

3. A 38-year-old man complains weight loss and night sweats. His history includes smoking one pack of cigarettes per day for about 20 years. On physical examination, you observe corrugated, well-defined white patches on the ventrolateral tongue, bilaterally. Which of the following is the most appropriate recommendation?

- A. Refer the patient for biopsy of the lingual lesions to exclude dysplasia or carcinoma.
- B. Advise the patient to discontinue smoking.
- C. Request a complete blood count and HIV test, then have the lesions biopsied.
- D. Have him return in 1 month to see if the lesions resolve spontaneously.
- E. Search for causes of chronic trauma.

Answer: C Although discontinuance of smoking is always good advice, many oral mucosal lesions are not associated with tobacco consumption. This case may represent oral hairy leukoplakia, an Epstein-Barr virus (which can be identified in the biopsy specimen) lesion and a manifestation of systemic HIV infection. These are uncommon lesions and are associated with a high HIV viral load; clinical suspicion should encourage further search for other HIV-related symptoms or signs.

4. A 52-year-old woman complains of dry mouth of long duration. She is taking five prescription medications, two of which have anticholinergic effects, and her affect suggests clinical depression. On examination, palpation of the four major salivary glands exhibits slight to mild induration. Which of the following is the most appropriate recommendation?

- A. Perform or refer the patient for a labial salivary gland biopsy to consider the salivary component of Sjögren's syndrome.
- B. Replace the two prescription drugs with alternatives that have less or no anticholinergic effects.
- C. Refer the patient for specialty management of her depression.
- D. Include rheumatoid factor (RF) and antinuclear antibody (ANA) titer in your laboratory request to consider the serologic component of Sjögren's syndrome.
- E. Perform an unanesthetized Schirmer tear test to consider the ocular component of Sjögren's syndrome.

Answer: A Although the patient's symptoms may be caused by the side effects of anticholinergic drugs, palpable salivary induration raises the suspicion of inflammation within them. Sjögren's syndrome is high on the differential diagnosis and is an indication for labial salivary gland biopsy. Positive RF and ANA are usually seen in patients with Sjögren's syndrome, but they lack specificity, even if both are positive. Positive anti-SS-A/SS-B serology can represent the serologic component of Sjögren's syndrome but is insufficient alone. A positive Schirmer test is currently insufficient to identify the ocular component of Sjögren's syndrome.

5. Examination of an asymptomatic 27-year-old male nonsmoker reveals numerous circular white lesions surrounding red atrophic patches on the dorsum of the tongue. The lesions cannot be rubbed off with a gauze square. The patient most likely has which of the following?

- A. Fissured tongue
- B. Speckled leukoplakia
- C. Benign migratory glossitis (geographic tongue)
- D. Squamous cell carcinoma
- E. Lichen planus

Answer: C The patient has geographic tongue, a harmless and common condition that results in transient depapillation of the tongue with a surrounding white halo. Over the course of several weeks, the depapillated area returns to normal. However, other areas may become affected, thereby giving the patient the perception that the lesion is migrating over the tongue. Despite its superficial resemblance to psoriasis, microscopically there is no relation. For the symptomatic patient, bland mouth rinses (baking soda in warm water, salt water) may provide symptomatic relief. Antifungal treatments are not recommended. There is no association with oral cancer.

1. A patient without other systemic disease or immunocompromise presents with otitis externa confined to the external auditory canal. Which of the following interventions would be recommended?

- A. The physician should prescribe an oral quinolone antibiotic.
- B. The physician should order a computed tomographic scan with contrast of the temporal bone.
- C. The physician should prescribe topical antibiotics.
- D. The physician should obtain a neurosurgical consult.
- E. The physician should recommend oral steroid medication.

Answer: C Otitis externa or "swimmer's ear" usually responds to topical antibiotic treatment. Oral or systemic antibiotics are specifically not recommended unless the patient is immunocompromised or the infection is spreading to the pinna cartilage of the external ear outside of the external auditory canal.

2. A patient presents to your office with recurrent epistaxis. A crust on the anterior septum is identified on the side of greatest bleeding. There is no active bleeding during the visit. The best course of action is which of the following choices?

- A. The patient should be admitted to the hospital for interventional embolization of the internal maxillary artery.
- B. The patient should be electively scheduled for a computed tomographic angiogram.
- C. The patient should be given a prescription for a β -blocker.
- D. The patient should be queried about aspirin use and be asked to take an "aspirin holiday."
- E. A bone marrow biopsy should be obtained.

Answer: D Patients with epistaxis are often on antiplatelet drugs for a variety of reasons. On intake history, use of nonsteroidal anti-inflammatory drugs should be specifically sought because curtailing antiplatelet medication will often eliminate troublesome epistaxis.

3. An adult patient presents with left ear pain but no hearing loss, beginning 4 weeks ago and partially controlled with narcotic pain medication. On physical examination, there is no evidence of otitis externa or otitis media. Which of the following choices is the best next step?

- A. A smoking history should be obtained, a neck examination should be performed, and the patient should be referred for upper airway endoscopic examination.
- B. An empirical trial of oral antibiotics should be prescribed for presumptive otitis media.
- C. An empirical trial of topical antibiotics should be prescribed for presumptive otitis externa.
- D. A magnetic resonance image of the brain and temporal bone, with contrast, should be ordered.
- E. The patient should be sent for a hearing test.

Answer: A Unexplained unilateral otalgia may be a referred pain from an upper aerodigestive tract lesion. Physical examination of the oral cavity, oropharynx, larynx, and hypopharynx should be performed. Tumors of the upper aerodigestive tract often present with an easily palpable, metastatic lymph node in the neck. Smoking, alcohol use, and human papillomavirus infection are risk factors for head and neck cancer.

4. A patient presents with nasal polyps visible on anterior rhinoscopy and also notes a history of asthma exacerbated by nonsteroidal anti-inflammatory drug use. What is the best treatment recommendation?

- A. The patient should be scheduled for nasal surgery.
- B. The patient should be scheduled for computed tomographic imaging of the sinuses.
- C. The patient should be given a prescription for ciprofloxacin.
- D. The patient should be scheduled for a sweat chloride test.
- E. The patient should be given an oral prednisone taper.

Answer: E This patient likely has aspirin exacerbated respiratory disease, also called Samter's triad or "aspirin allergy." Oral corticosteroids can shrink nasal polyps and help control symptoms in patients with this disorder.

5. A patient presents to your office with a 4-day history of an upper respiratory infection that has prevented attendance at school. The physician should take which of the following steps?

- A. The history suggests chronic infection, and the patient should be given oral antibiotics.
- B. The history suggests acute infection, and the patient should be given oral antibiotics.
- C. The history is consistent with a viral upper respiratory infection, and symptomatic treatment should be recommended.
- D. The patient should be given a prescription for topical antifungal medication.
- E. None of the above

Answer: C Several meta-analyses have shown that oral antibiotics or topical antibiotics provide no meaningful improvement in sinusitis during the first 7 to 10 days of treatment. Supportive care is the best option; it should include decongestants, hydration, fever control with antipyretics, and patience in allowing the symptoms to resolve.

1. A 53-year-old woman being treated for metastatic breast cancer complains of loss of taste. Which of the following is least likely to explain the taste loss?

- A. Radiation therapy
- B. Poor nutrition
- C. Chemotherapy
- D. Age
- E. Hormonal changes

Answer: D Although age can lead to minor deficits in taste because of decreased turnover in taste bud cells, age would not be likely to explain taste loss in this relatively young woman. A, B, C, and E can cause severe loss of taste, particularly in this clinical circumstance.

2. A 39-year-old woman presents with subacute onset of loss of smell. What is the most likely cause?

- A. Head trauma
- B. Viral infection
- C. Vitamin deficiency
- D. Multiple sclerosis
- E. Sinusitis

Answer: B Viral infections are the most common cause of loss of smell. The other conditions also can cause loss of smell but are less likely.

3. A 42-year-old man presents with subacute onset of hemifacial paralysis and persistent taste of sweetness. What clinical feature is not consistent with Bell's palsy (VII cranial nerve palsy)?

- A. Hemifacial paralysis
- B. Loss of taste in the anterior two thirds of the tongue
- C. Persistent taste of sweetness
- D. Intact taste in the posterior third of the tongue
- E. Drooling or dry mouth with difficulty in eating

Answer: C A major branch of the mastoid segment of cranial nerve VII is the chorda tympani, which contains afferent taste fibers from the anterior two thirds of the tongue and is the anatomic basis for the loss of taste in the anterior two thirds of the tongue in idiopathic cranial nerve VII palsy. In contrast with loss of taste, a persistent sense of sweetness is a worrisome symptom for an irritative lesion, such as a neoplastic, inflammatory, or demyelinating lesion involving cranial nerve VII.

4. What is the molecular basis that allows us to taste carbonation in sodas, sparkling wines, and other carbonated drinks?

- A. G protein–coupled glutamate receptor for umami
- B. Carbonic anhydrase IV expressed on the surface of sour-sensing cells
- C. TAS1R heterodimers for sweetness
- D. TAS2R proteins for bitter taste
- E. Epithelial sodium channel receptor for salty taste

Answer: B Mountaineers who take acetazolamide (a carbonic anhydrase inhibitor) to prevent altitude sickness have long reported that carbonated beverages lacked pleasurable taste or tingle sensation. Patients treated with acetazolamide and other medications with carbonic anhydrase–inhibiting activities also experience taste disturbances.

1. Which of the following would not be typical of a conductive hearing loss?

- A. Marked improvement with amplification
- B. Ability to hear speech in a noisy background
- C. Relatively maintained speech recognition
- D. Loud speech is annoying
- E. Bone greater than air conduction

Answer: D Patients with conductive hearing loss prefer loud speech, which they can understand as well as normal people can. A, B, C, and E are typical for conductive hearing loss.

2. Which of the following diagnoses would be least likely to be manifested with a unilateral hearing loss?

- A. Acoustic neuroma
- B. Meniere disease
- C. Otosclerosis
- D. Brain stem glioma
- E. Otitis media

Answer: D Brain stem lesions rarely cause unilateral hearing loss unless they involve the root entry zone of the cochlear nerve. Otosclerosis is usually bilateral but often begins unilaterally. The other conditions are typically unilateral.

3. Which of the following is least likely to be manifested with vertigo?

- A. Acoustic neuroma
- B. Meniere disease
- C. Lateral medullary infarction
- D. Migraine
- E. Vestibular neuritis

Answer: A Acoustic neuroma typically is manifested with unilateral hearing loss or tinnitus. It compresses the vestibular nerve slowly, so central compensation can occur. It rarely is manifested with vertigo. B, C, D, and E commonly are manifested with vertigo.

4. Which of the following would be an unusual precipitant for benign paroxysmal positional vertigo?

- A. Turning in bed
- B. Yoga class
- C. Driving
- D. Reaching for something on a high shelf
- E. Working under an automobile

Answer: C Benign paroxysmal positional vertigo is typically triggered by movement in the vertical plane (plane of the posterior semicircular canal). It would be unusual to make such a movement while driving. The other maneuvers are common precipitating circumstances.

5. Which of the following would most likely be associated with a positive head-thrust test result?

- A. Meniere disease
- B. Lateral medullary infarction
- C. Cerebellar infarction
- D. Gentamicin ototoxicity
- E. Otitis media

Answer: D Gentamicin is remarkably selective for the vestibular system, and the head-thrust test is useful for identifying toxicity at the bedside. The head-thrust test result is rarely positive with Meniere disease and would be negative with lateral medullary infarction, cerebellar infarction, and otitis media.

Ch / 430 **PRINCIPLES OF MEDICAL CONSULTATION**

1. Your hospital seeks your advice on the development of a comanagement model between internal medicine and the inpatient orthopedic service. Which of the following strategies will provide the most optimal comanagement?

- A. Internists and orthopedists round together in the morning along with nursing staff.
- B. Orthopedists write all orders.
- C. Internists consult only when a postoperative medical complication occurs.
- D. Primary care physician determines whether comanagement is necessary.

Answer: A Comanagement is a strategy in which all patients on a particular service, usually a surgical service such as orthopedics, receive a mandatory internal medicine consult. In most instances, hospitalists provide this service. The intent is to provide optimal postoperative care in order to prevent, rather than simply to treat, complications. Both the consulting internist and the surgeon may write orders. Optimally, both services round together in the morning to identify patient management issues and to establish the daily plan along with the assistance of the nursing staff.

2. Rapid response teams exist to prevent “failure to rescue” on inpatient non-intensive care unit (ICU) services. Which of the following represents an appropriate trigger to call a rapid response team?

- A. Systolic blood pressure of 110 mm Hg
- B. Oxygen saturation of 82% on room air
- C. Temperature of 101.5° F
- D. More than 5 ectopic ventricular beats per minute

Answer: B Rapid response teams are an example of a consultation team. Their purpose is to prevent “failure to rescue,” reduce unplanned ICU transfers, and hopefully reduce in-hospital mortality. Certain triggers automatically initiate a request for consultation. The most important of these are critical vital sign values and respiratory distress. In this example, oxygen desaturation is a trigger. Fever alone warrants clinical evaluation but is not a trigger in the absence of other features.

3. Which of the following strategies does *not* improve adherence to a consultant’s recommendations?

- A. Limit recommendations to less than five
- B. Provide contingency plans for potential clinical scenarios
- C. Make a direct call to requesting physician to discuss care plans
- D. Provide literature references
- E. Determine the question

Answer: D Substantial literature provides guidance on strategies to improve adherence to a consultant’s recommendations and thus to improve patient care. Consultations that are concise, with a limited number of key recommendations, are most likely to be followed. Contingency plans outline steps that the requesting doctor should take in the event of certain changes in clinical condition. It is critical to understand the question. If the requesting and consulting physician do not agree on or understand the question, the consult is doomed to be unhelpful. Requesting physicians are generally uninterested in literature references to support the recommendations of the consultant.

4. When performing a preoperative medical consultation, the consultant identifies risk factors for postoperative medical complications. The consultant should do which of the following?

- A. Clear the patient for surgery
- B. Advise the patient to forgo surgery
- C. Determine the impact of the risk factor and propose strategies to reduce the risk
- D. Request another consultation from a subspecialist

Answer: C A consultant should never “clear” a patient before surgery. Such a message may imply zero risk and fails to consider the impact of particular risk factors. Rather, the appropriate approach is to determine what factors may increase risk, estimate overall risk, and then propose strategies to reduce risk. The goal is for the patient to be in the best possible condition before surgery. The consulting medical physician’s primary responsibility is to the requesting physician. The consultant should not directly advise the patient to forgo surgery. Rather, the consultant should share any concerns with the requesting surgeon and develop a collaborative plan. If the consultant determines that a subspecialty consultation is warranted, he or she should suggest that to the surgeon but should not directly obtain another consultation without first obtaining agreement from the surgeon.

5. Your primary care colleague asks you for a curbside consultation in infectious disease. You have not met the patient. Your consultation will achieve which of the following?

- A. Improve patient care
- B. Expose you to unnecessary medicolegal risk
- C. Be based on an accurate and complete patient history
- D. Generate income as an evaluation and management (E&M) activity

Answer: A Curbside consultations are a common and important activity for consultants, particularly in “cognitive” specialties in which the consultant does not commonly perform procedures. The consultant has no doctor-patient relationship. Therefore, most courts have held that there is no medicolegal risk to the consultant. When a formal consultation follows, it is often true that additional elements emerge from the history and physical examination. Despite this limitation, curbside consultations improve both access to subspecialty care and patient care. Unfortunately, curbside consultations are not generally billable activities; however, approximately one third of curbside consultations result in a request for a formal, billable consultation.

Ch / 431 PREOPERATIVE EVALUATION

1. A 70-year-old man is scheduled for cataract surgery. Past medical history includes hypertension, hyperlipidemia, and coronary artery disease with a myocardial infarction 10 years ago. He has been asymptomatic since then but has a sedentary lifestyle. He is a former smoker. Medications include aspirin, metoprolol, and atorvastatin. He denies chest pain or dyspnea. Vital signs and physical examination are within normal limits. His electrocardiogram at the time of his last visit 3 months ago showed normal sinus rhythm with left ventricular hypertrophy and evidence of an old inferior wall myocardial infarction. Which of the following would you recommend preoperatively?

- A. Basic metabolic panel (electrolytes, renal function, glucose)
- B. Electrocardiogram
- C. Hemoglobin
- D. Stress test
- E. No further testing

Answer: E Despite having multiple risk factors, the patient is undergoing a low-risk procedure, and no further testing would be helpful. His risk for major cardiac complications is less than 1%, and the procedure is not associated with any significant hemodynamic changes or blood loss. Therefore, even an abnormal result (anemia, chronic kidney disease, hyperglycemia) would be unlikely to change

management. (Keay L, Lindsley K, Tielsch J, et al. Routine preoperative medical testing for cataract surgery. *Cochrane Database Syst Rev.* 2012;3:CD007293.)

2. A 60-year-old man is scheduled for colonoscopy and polypectomy. His medical history is pertinent for hypertension, diabetes mellitus, and atrial fibrillation, and he is taking warfarin, metformin, and amlodipine. Which of the following would you recommend regarding perioperative anticoagulation management?

- A. Continue warfarin
- B. Continue warfarin but give fresh-frozen plasma 2 hours before surgery
- C. Stop warfarin 5 days before surgery
- D. Stop warfarin 5 days before surgery and “bridge” with low-molecular-weight heparin preoperatively
- E. Stop warfarin 5 days before surgery and “bridge” with low-molecular-weight heparin preoperatively and postoperatively

Answer: C In general, warfarin needs to be stopped before a polypectomy. This patient has a CHADS2 score of 2, in which case the risk for thromboembolism is low if temporarily stopping warfarin. Furthermore, if full-dose anticoagulation is started too early after the procedure, there is an increased risk for bleeding. The American College of Chest Physicians guidelines recommend stopping warfarin 5 days before the procedure (to allow the international normalized ratio to drop below 1.5) without the need for bridging therapy in this case. (Douketis JD, Spyropoulos AC, Spencer FA, et al; American College of Chest Physicians. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141[2 Suppl]:e326S-50S. Erratum in: *Chest.* 2012; 141:1129.)

3. A 60-year-old woman is seen preoperatively before a vaginal hysterectomy. She has hypertension, diabetes, chronic kidney disease, and coronary artery disease but no history of myocardial infarction, recent chest pain, or dyspnea. She walks 1 mile 3 times a week and can climb 2 flights of stairs without symptoms. She states she had a negative stress test 5 years ago. She is taking aspirin, nitrates, metoprolol, lisinopril, furosemide, and insulin. Her physical examination is unremarkable, and her preoperative test results are: glucose 150 mg/dL, blood urea nitrogen 40/creatinine 2.1. Her electrocardiogram shows normal sinus rhythm with no ischemic changes. Which of the following would you recommend preoperatively?

- A. Brain natriuretic peptide
- B. Two-dimensional echocardiogram
- C. Exercise electrocardiogram
- D. Pharmacologic stress test (nuclear or echo)
- E. No further testing

Answer: E Although she has a revised cardiac risk index score of 3, she has no active cardiac conditions and has a functional capacity of >4 MET, so no further cardiac testing is necessary. Although an elevated preoperative (or postoperative) brain natriuretic peptide level may be associated with an increased risk for complications, the procedural risk is not high, and there is no evidence that any intervention will improve her outcome. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA Guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014;130:2215-2245.

4. A 70-year-old man is scheduled to undergo an elective total hip replacement for severe osteoarthritis, which limits his activity. He has coronary artery disease and had a drug eluting stent (DES) placed in his proximal left anterior descending coronary artery 3 months ago. He is on aspirin and clopidogrel and has had no chest pain or dyspnea since the stent placement. Which of the following would you recommend?

- A. Proceed to surgery; continue aspirin and clopidogrel
- B. Proceed to surgery; continue aspirin; stop clopidogrel 5-7 days preoperatively
- C. Proceed to surgery; continue clopidogrel; stop aspirin 5-7 days before surgery
- D. Proceed to surgery; stop both aspirin and clopidogrel 5-7 days before
- E. Postpone surgery for at least 3 months; continue aspirin and clopidogrel

Answer: E Current guidelines recommend continuing uninterrupted dual antiplatelet therapy for at least 6 if not 12 months after placement of a DES to minimize the chance of in-stent thrombosis.

Although the newest generation of DES may require shorter durations of antiplatelet therapy, at the current time elective surgery should be postponed for at least 6 and preferably 12 months in order to complete the recommended course of uninterrupted dual antiplatelet therapy. At that time, a decision can be made about whether to continue both drugs or to continue just aspirin, which is continued for life. (Darvish-Kazem S, Gandhi M, Marcucci M, Douketis JD. Perioperative management of antiplatelet therapy in patients with a coronary stent who need non-cardiac surgery: a systematic review of clinical practice guidelines. *Chest*. 2013;144:1848-1856.)

Ch / 432 OVERVIEW OF ANESTHESIA

1. A 75-year-old healthy woman asks your opinion if she should undergo an elective back operation. She is concerned about her perioperative risks for mortality. You tell her that her that perioperative mortality is mostly determined by which of the following?

- A. Patient's underlying medical problems
- B. The surgical procedure
- C. The anesthetic
- D. The volume of procedures done at a hospital

Answer: A.

2. A 55-year-old woman comes to you for a preoperative assessment. She has a long history of refractory depression. You inquire whether she is on monoamine oxidase inhibitors, so your list of medications should include which of the following?

- A. Selegiline
- B. Moclobemide
- C. Pargyline
- D. Isoniazid

Answer: All are correct. See Gillman PK. Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity. *Br J Anaesth*. 2005;95:434-441.

3. You are treating a 35-year-old man who is on chronic opioids for pain. He comes into the hospital with a broken limb, and his pain is not adequately treated despite increasing doses of opioid analgesics. You suggest ketamine because it will do all of the following except which one?

- A. Decrease the need for opioids
- B. Provide analgesia
- C. Improve sedation
- D. Decrease respiration

Answer is D. Ketamine preserves respiration.

1. An 83-year-old woman who fell in a nursing home is admitted because she now is unable to walk. The diagnosis is a hip fracture, and the plan is for surgical repair. She is taking multiple chronic medications that might be sources of drug toxicity if surgery leads to changes in liver function, kidney function, oral intake, or drug-drug interactions. Which of the following medications, however, would not merit careful monitoring and dose adjustment during the perioperative interval?

- A. L-Thyroxine
- B. Lithium
- C. Phenytoin
- D. Cyclosporine
- E. Metoprolol

Answer: A Changes in drug absorption and elimination lead to large changes in the pharmacodynamics of most medications. As a consequence, routine measurement of lithium levels, phenytoin levels, and cyclosporine levels is indicated in patients receiving such medications. Doses of β -blockers, such as metoprolol, may also need to be adjusted on the basis of the patient's heart rate and blood pressure. One exception is that thyroid supplements, such as l-thyroxine, do not typically require monitoring and adjustment.

2. A 72-year-old man has been diagnosed with ocular cataracts and is awaiting carotid endarterectomy surgery. His list of medications needs to be reviewed to distinguish drugs that are essential in the postoperative setting from other drugs that are counterproductive (or superfluous) in the postoperative setting. Which of the following chronic medications should *not* be routinely discontinued in this patient?

- A. Alendronate
- B. Calcium carbonate
- C. Iron sulfate
- D. Ginkgo biloba
- E. Aspirin

Answer: E The patient is receiving multiple medications that are often available without a prescription in some countries. Each is relatively safe among otherwise healthy outpatients, can cause problems in patients who are recovering from surgery, and is a long-acting metabolic agent that could be discontinued with no immediate withdrawal syndrome. Calcium carbonate is typically formulated in large pills that might be aspirated in the immediate postoperative setting. Iron sulfate might worsen postoperative gastritis even though it was tolerated on an outpatient basis. Ginkgo biloba can increase the risk of postoperative hepatitis when it is taken in the perioperative setting. Alendronate can lead to hemorrhagic esophagitis arising from impaired swallowing after surgery. Aspirin is the major exception with this particular operation, in which randomized trials suggest a significantly reduced risk of a postoperative stroke after carotid surgery that outweighs the risk of a secondary gastrointestinal tract hemorrhage.

3. A 94-year-old woman presents with postmenopausal painless vaginal bleeding. Her baseline functional status is excellent, and she walks half an hour each day for exercise. The diagnosis is endometrial cancer, and she undergoes a total abdominal hysterectomy. On the first day after surgery, she develops delirium characterized as a hypoactive state with no oral intake, simple one-word verbal responses to questioning, and an inability to follow simple commands. Which of the following would *not* be a contributing cause to her delirium?

- A. Carbon dioxide narcosis
- B. Adverse drug reaction
- C. Hypothyroidism
- D. Alcohol withdrawal syndrome

E. Surgical site infection

Answer: C The patient has developed an acute postoperative delirium with no clear localizing findings.

An adverse drug reaction is a leading consideration because of drug-drug interactions, altered pharmacokinetics, or other mechanisms. Carbon dioxide narcosis is a possibility, particularly if the patient has undiagnosed sleep apnea, respiratory depression with analgesia, and pulmonary atelectasis after abdominal surgery. Alcohol withdrawal with hypoactive delirium tremens is also a potential, as is an occult surgical site infection. Hypothyroidism, however, rarely is a major contributor to acute delirium. Therefore, hypothyroidism is one factor that is unlikely to explain postoperative delirium.

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MEDICAL CONSULTATION IN PSYCHIATRY

1. Medical deterioration during psychiatric admissions may lead to life-threatening complications, interrupt biobehavioral interventions, and require transfer to medical facilities. Older age and a diagnosis of dementia with behavioral disturbance are nonmodifiable correlates of an increased rate of acute changes in medical conditions in psychiatric patients. Which of the following is an independent risk factor for medical deterioration in psychiatric settings?

- A. Blood urea nitrogen concentration (higher)
- B. Congestive heart failure
- C. Serum potassium concentration (lower)
- D. Serum sodium concentration (lower)
- E. Substance use disorder

Answer: A Among 1000 adults consecutively admitted to a free-standing psychiatric hospital, 14% were transferred to a general hospital for acute medical deterioration. The independent predictors of medical deteriorations were higher blood urea nitrogen concentration (odds ratio, 63.2), lower hemoglobin level (odds ratio, 35.3), and lower albumin level (odds ratio, 7.3). (Manu P, Asif M, Khan S, et al. Risk factors for medical deterioration of psychiatric inpatients: opportunities for early recognition and prevention. *Compr Psychiatry*. 2012;53:968-974.)

2. The 27-year-old with clozapine-treated schizophrenia admitted for suicidal ideation is prescribed venlafaxine 37.5 mg/day, which is rapidly increased to 150 mg/day without adverse drug reactions. An episode of severe agitation is treated with aripiprazole 9.75 mg administered intramuscularly. The following morning, the patient has good behavioral control and is allowed to play basketball on the outdoor court for 45 minutes. He then becomes febrile (39.1° C) and has two episodes of nonbloody diarrhea. The physical examination is significant for mild and diffuse muscle rigidity, diaphoresis, and ankle clonus. The white blood cell count is 10,200 with an absolute neutrophil count of 4800; the creatine kinase level is 380. The electrolyte values and urinalysis are normal. What is the most likely cause of the febrile syndrome?

- A. Neuroleptic malignant syndrome
- B. Eosinophilic colitis
- C. Viral gastroenteritis and neuroleptic-induced Parkinsonism
- D. Serotonin syndrome
- E. Heat stroke

Answer: D Serotonin syndrome may develop rapidly after the addition of an antipsychotic (aripiprazole) with serotonergic enhancing properties in patients treated with a dual (serotonin and norepinephrine) reuptake antidepressant drug (venlafaxine). Some of its clinical features, (e.g., diarrhea and clonus) are not seen in neuroleptic malignant syndrome. (Perry PJ, Wilborn CA. Serotonin syndrome vs neuroleptic malignant syndrome: a contrast of causes, diagnoses, and management. *Ann Clin Psychiatry*. 2012;24: 155-162.)

1. The proliferative layer of the epidermis is the _____.

- A. Basal layer.
- B. Spinous layer.
- C. Granular layer.
- D. Stratum corneum.
- E. Stratum lucidum

Answer: A The basal layer is the most undifferentiated layer of the epidermis and the layer in which most proliferation occurs. The other, more superficial layers of the epidermis are formed from keratinocytic differentiation. The stratum lucidum is a compact layer between the granular layer and stratum corneum and is present only in palmoplantar skin.

2. Marfan syndrome is caused by a mutation in the gene encoding _____.

- A. Elastin
- B. Fibrillin-1
- C. Elaunin
- D. Type I procollagen
- E. Type V collagen

Answer: B Mutations in fibrillin-1 cause Marfan syndrome. Mutations in elastin result in cutis laxa. Elaunin is an elastic fiber component that does not have a described genodermatosis. Mutations in type I procollagen cause osteogenesis imperfecta, whereas mutations in type V collagen can result in Ehlers-Danlos syndrome.

3. Which of the following does *not* play a role in the pathogenesis of itch?

- A. Dorsal root ganglion
- B. Thalamus
- C. Pituitary gland
- D. Spinothalamic tract neurons
- E. Free nerve endings

Answer: C The pituitary gland is not involved in the itch pathway. The other choices are all found along the pathway for itch perception between the free nerve endings of the skin and the processing centers in the brain.

4. Defects in all of the following proteins can cause blistering diseases *except*:

- A. Keratin 5
- B. Laminin 332
- C. Filaggrin
- D. Collagen VII
- E. Plectin

Answer: C Defects in filaggrin can lead to ichthyosis and atopic dermatitis, but not a blistering disease. Defects in keratin 5 and plectin can cause epidermolysis bullosa simplex. Mutations in laminin 332 can cause junctional epidermolysis bullosa. Collagen VII forms anchoring fibrils, defects in which can cause dystrophic epidermolysis bullosa.

1. A 48-year-old man comes to the emergency room complaining of 2 days of excruciating stabbing pain and tenderness behind his right ear. There is no history of trauma. The pain keeps him up at night. He is healthy otherwise. Your examination reveals exquisite tenderness on the occipital scalp behind his right ear and extending to parietal scalp, but there are no other cutaneous findings. The most likely diagnosis is:

- A. Erysipelas.
- B. Herpes simplex.
- C. Herpes zoster.
- D. Malingering.
- E. Meningitis.

Answer: C Pain involving the skin or scalp eliminates intracranial disease. Herpes zoster classically causes pain along part or all of a dermatome several days before lesions become apparent on the skin. Malingering is always a consideration when no physical findings are present, but careful examination usually can delineate the margins of tenderness accurately.

2. A 52-year-old man is transferred to your hospital with fever, severe malaise, and sharp right upper quadrant pain. For the last 4 years, he has been on low-dose methotrexate for rheumatoid arthritis. He also has taken occasional nonsteroidal anti-inflammatory drugs for pain. Imaging at a community hospital revealed no anatomic liver pathology, but blood work showed elevated liver enzymes. On examination he has ill-defined right upper quadrant tenderness with no obvious hepatomegaly and a nonsurgical abdomen. On examination of his skin, you notice approximately 50 individual raised vesicles, each the size of a pea, on his trunk and extremities. Some lesions are crusted, some appear hemorrhagic, some contain clear fluid, and some have an umbilicated appearance. Mucosal surfaces are normal.

3. In the patient in question 2, what diagnosis is *least* likely?

- A. Disseminated candidiasis
- B. Disseminated varicella-zoster virus
- C. Rocky Mountain spotted fever
- D. Erythema multiforme
- E. Toxic epidermal necrolysis

Answer: E Toxic epidermal necrolysis (TEN) could manifest with symptoms of fever and malaise, but the morphology of multiple individual discrete lesions and the absence of mucosal involvement make TEN highly unlikely.

4. In the patient in question 2, what diagnosis is *most* likely?

- A. Disseminated candidiasis
- B. Disseminated varicella-zoster virus
- C. Rocky Mountain spotted fever
- D. Erythema multiforme
- E. Toxic epidermal necrolysis

Answer: B Disseminated varicella-zoster virus is most likely. The multiple widely spread lesions, some of which are umbilicated, favor a disseminated viral infection. The right upper quadrant pain represents dermatomal pain from herpes-zoster viral reactivation, but without dermatomal skin findings.

5. A 25-year-old woman comes to your office complaining of 2 days of sore throat, as well as severe redness and soreness of her lips, the inside of her mouth, her eyes, and her anogenital region. Painful sores on her palms and soles developed in the last 24 hours. She denies fever but complains of coughing. She attributes the skin problem to her recent urinary tract infection, for which she was given trimethoprim-sulfamethoxazole 7 days earlier. Your examination shows confluent erosions on the oral, anogenital, and conjunctival mucosae. Palm lesions consist of numerous tender erythematous macules. What is the *most* threatening diagnosis to consider and treat immediately?

- A. Kawasaki's disease
- B. Toxic shock syndrome
- C. Toxic epidermal necrolysis
- D. Staphylococcal scalded skin syndrome
- E. Glucagonoma syndrome

Answer: C Erosive mucositis is the key morphology here. In patients with acute erosive mucositis, especially at multiple sites, the first diagnosis to consider is toxic epidermal necrolysis or its slightly less severe variant, Stevens-Johnson syndrome. In this case, in addition to mucositis, the drug history points to a possible severe drug eruption. Glucagonoma syndrome can manifest with mucosal erosions, but they are not acute. Kawasaki's disease and toxic shock syndrome manifest with erythema of the mucosae, but they rarely become erosive.

1. A clean ulcer that needs to granulate and re-epithelialize should be treated by:

- A. Moist wound healing with a topical ointment and dressing.
- B. Wet-to-dry dressing with dry gauze and no ointment.
- C. Being left open to heal.
- D. Oral antibiotics.
- E. Oral steroids.

Answer: A Moist wound healing is the standard for chronic wound management. Moist wounds heal two to three times faster than dry wounds. The primary purpose of wet-to-dry dressings is the mechanical débridement of necrotic tissue. Dried tissue is more prone to infection and pain, and it heals more slowly than if kept moist. A moist wound environment physiologically favors cell migration and matrix formation, while accelerating healing of wounds by promoting autolytic débridement.

2. The combination clotrimazole and betamethasone dipropionate topical therapy (lotrisone) is:

- A. More effective for fungal infections than clotrimazole alone.
- B. Safe for use in the groin and face
- C. Approved for use in children younger than 12 years of age.
- D. Should be used sparingly because of risks for thinning the skin and striae.
- E. Is effective against bacteria.

Answer: D Fluorinated topical steroids are potent and cause thinning of the skin and striae. As a result, they should not be used in areas where the skin is thin, such as the face, or where the area is occluded and increases absorption in the skin, such as the groin. It is preferable to treat fungal infections with an antifungal agent, and if a topical anti-inflammatory steroid is also desired, a separate treatment with a mild lower class steroid may be used.

3. Topical antibiotics as a solitary agent for acne for more than 3 months is not recommended because:
- A. Increased risk of drug toxicity.
 - B. Higher incidence of bacterial resistance after that time.
 - C. Effects on thinning of skin.
 - D. It should not be combined with other therapies.
 - E. It causes photosensitivity.

Answer: B When topical antibiotics are used in combination with benzoyl peroxide, there is reduced emergence of resistant strains of *Propionibacterium acnes*.

4. People starting a TNF blocker or other biologic therapy should be tested to exclude:
- A. Heart disease.
 - B. Underlying malignancy.
 - C. Lung disease.
 - D. Atherosclerosis.
 - E. Tuberculosis.

Answer: E The biologics are immunosuppressants that facilitate reactivation of tuberculosis, which can then disseminate. Unless a person has a history of a positive test followed by appropriate treatment, routine tuberculosis testing is recommended, either by PPD or quantiferon gold testing.

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ECZEMAS, PHOTODERMATOSES, PAPULOSQUAMOUS (INCLUDING FUNGAL) DISEASES, AND FIGURATE ERYTHEMAS

1. A 16-year-old high school student presented with pruritic, lichenified plaques on her antecubital and popliteal fossa and dryness of skin. The first-line treatment is:
- A. Cyclosporin 100 mg twice daily.
 - B. Narrow band ultraviolet light B therapy.
 - C. Oral prednisone 40 mg/day.
 - D. Psoralen and UVA (PUVA) photochemotherapy.
 - E. Triamcinolone ointment 0.1% twice daily.

Answer: E This is a case of atopic dermatitis, for which topical corticosteroids are first-line therapy. The next steps in the therapeutic ladder are narrow band UVB phototherapy (a benign treatment, but the patient needs to go to phototherapy center 2 to 3 times per week) and PUVA (potential photocarcinogenesis with long-term treatment is a drawback, especially for a 16-year-old patient). Cyclosporine and oral prednisone should be reserved for recalcitrant cases because of their side effects.

2. A 23-year-old otherwise healthy African American woman sees you 2 days after she spent a week in Hawaii. A few days after she arrived in Hawaii, she developed minimally pruritic 1- to 2-mm papules on her extensor forearm and on the dorsum of her hands. The most likely diagnosis is:
- A. Chronic actinic dermatitis.
 - B. Drug-induced phototoxicity.
 - C. Erythropoietic protoporphyria.
 - D. Polymorphic light eruption.
 - E. Porphyria cutanea tarda.

Answer: D Pinhead papular eruption is the typical morphology of polymorphic light eruption in dark-skinned individuals. Chronic actinic dermatitis presents with chronic photosensitivity and lichenification on sun-exposed areas. Drug-induced phototoxicity can be excluded by the history.

Erythropoietic protoporphyria is a chronic photosensitivity, which typically starts in childhood. Porphyrria cutanea tarda manifests with skin fragility, blisters, and erosions on a sun-exposed area.

3. A 55-year-old man with a long history of psoriasis presents with a 2-week history of worsening skin lesions and generalized erythroderma. The single most appropriate treatment is:

- A. Calcipotriene cream 0.005% twice daily.
- B. Cyclosporin 100 mg twice daily.
- C. Tazarotene cream 0.1% twice daily.
- D. Triamcinolone ointment 0.1% daily.
- E. Prednisone 60 mg/day.

Answer: B Topical treatments (calcipotriene cream, tazarotene cream, triamcinolone ointment) are not sufficient to suppress active disease in rapidly progressing, erythrodermic psoriasis. Oral cyclosporine is a fast-acting medication with a well-documented efficacy for this condition. Oral prednisone should not be used because psoriasis can flare significantly when it is tapered.

4. An otherwise healthy 38-year-old man presents with a 1-month history of generalized erythroderma with salmon-colored and fine scaling, several areas of sparing on his abdomen and upper back, ectropion and keratoderma of palms and soles. The most likely diagnosis is:

- A. Erythrodermic mycosis fungoides.
- B. Pityriasis lichenoides chronica.
- C. Pityriasis rosea.
- D. Pityriasis rubra pilaris.
- E. Erythrodermic psoriasis.

Answer: D Salmon-colored erythroderma, “islands of sparing,” and keratoderma of the palms and soles are the characteristic morphology of pityriasis rubra pilaris. Erythrodermic mycosis fungoides manifests with reddish-to-violaceous erythroderma; it does not typically have islands of sparing. Pityriasis lichenoides chronica manifests as scattered erythematous papules and plaques; it does not manifest as generalized erythroderma. Pityriasis rosea manifests with minimally erythematous patches with fine scales. Patients with erythrodermic psoriasis usually have areas of typical psoriasis (papules and plaques with micaceous scales on elbows, knees, scalp); they do not have islands of sparing.

5. A 66-year-old man presents with a 1-year history of several asymptomatic patches, 5 to 6 cm in diameter, epidermal atrophy on his buttocks, and several semicircular erythematous plaques with no scales on his arms and thighs. Biopsy of a plaque on his thigh will most like show:

- A. Atypical mononuclear cells in the epidermis, with a CD4 predominant infiltrate.
- B. Dense infiltrate of lymphocytes at dermal-epidermal junction (lichenoid infiltrate).
- C. Dermal-epidermal separation.
- D. Edema in the epidermis (spongiosis) and in the dermis.
- E. Necrotic keratinocytes in the epidermis.

Answer: A The other biopsy findings are typical of lichen planus (B), blistering skin diseases (C), dyshidrosis (D), and erythema multiforme (E).

1. Treatment of severe nodulocystic acne with which of the following vitamin derivatives may completely arrest the disease process through decreasing *Propionibacterium acnes*?

- A. Vitamin D
- B. Vitamin A
- C. Vitamin K
- D. Vitamin E
- E. Vitamin B3

Answer: B 13-cis-Retinoic acid (isotretinoin/Accutane) is a derivative of vitamin A. In acne, it rapidly suppresses sebum production, causing a decrease in *P. acnes* populations. It also decreases follicular plugging. Vitamins D, K, and E are fat-soluble vitamins that do not completely arrest the disease process in acne.

2. The most common extracutaneous complications of varicella zoster virus is

- A. lymphoreticular.
- B. musculoskeletal.
- C. cardiovascular.
- D. central nervous system.
- E. postherpetic neuralgia.

Answer: E Zoster usually resolves without sequelae in children and young adults with intact immune systems. However, the pain, cutaneous eruption, and complications of zoster become more severe with increasing age and immune compromise. Complications of zoster include postherpetic neuralgia, secondary bacterial infection, scarring, ophthalmic zoster, Ramsay-Hunt syndrome, meningoencephalitis, motor paralysis, pneumonitis, and hepatitis.

3. What is the following is the best first line choice for treatment of herpes zoster?

- A. Ganciclovir
- B. Foscarnet
- C. Valacyclovir
- D. Gabapentin
- E. Cidofovir

Answer: C First-line treatment of herpes zoster (shingles) is with valacyclovir, acyclovir, or famciclovir. Gabapentin may be used for postherpetic neuralgia. Cidofovir and ganciclovir are reasonable treatment options for cytomegalovirus. Foscarnet is used to treat acyclovir resistant herpes simplex infections.

4. What is the most common cause of erythema multiforme?

- A. Herpes simplex virus
- B. Mycoplasma pneumonia
- C. Amoxicillin
- D. Ibuprofen
- E. Cytomegalovirus

Answer: A The most common cause of erythema multiforme is herpes simplex virus, which may not be active at the time of the erythema multiforme eruption. Patients with recurrent erythema multiforme are typically treated with acyclovir or valacyclovir. Mycoplasma pneumonia is a less common cause of erythema multiforme. Amoxicillin, ibuprofen, and cytomegalovirus may cause erythema multiforme but are much less commonly associated with it than is herpes simplex virus.

Ch / 440 **URTICARIA, DRUG HYPERSENSITIVITY RASHES, NODULES AND TUMORS, AND ATROPHIC DISEASES**

1. A 45-year-old man with a history of atopic dermatitis in childhood presents with faint pink, slightly raised lesions for the past 10 weeks. He complains of epigastric pain and burning in his chest, typically occurring after eating a meal, for the past 3 months. He reports that the lesions come and go and do not persist for more than 24 hours. On physical examination, he has urticaria that blanches with pressure on his chest, back, and upper and lower extremities. What is the next step in management?

- A. Skin biopsy
- B. Begin intravenous (IV) methylprednisolone
- C. Begin cyclosporine
- D. Allergy testing
- E. *Helicobacter pylori* infection testing

Answer: E The lesions described above are classic for urticaria and would be considered chronic given the duration of more than 6 weeks. Chronic urticaria can be triggered by occult infections, such as *H. pylori*, so *H. pylori* infection should be evaluated first in this case. The patient's complaints of epigastric pain and burning suggest the possibility of gastroesophageal reflux disorder. He should be evaluated for *H. pylori* infection. Skin biopsy should be performed if urticarial lesions present for more than 24 hours to evaluate him for urticarial vasculitis. IV corticosteroids can be considered if the urticaria is severe or if it is associated with anaphylaxis or wheezing. If the history is not suggestive of a trigger, allergy testing is recommended.

Chronic urticaria (Chapter 440).

2. A 25-year-old white woman with seizures presents to her primary care physician with a generalized symmetrical rash that started 1 week ago. She had her first seizure 6 weeks ago, at which time she was started on carbamazepine, which controlled her seizures. Vital signs reveal blood pressure, 119/60; heart rate, 105 beats/min; respiratory rate, 14 breaths/min; temperature, 100.9° F; and oxygen saturation, 99% on room air. Physical examination reveals normal conjunctivae and oropharynx, but she has erythroderma, and pustules present diffusely. Laboratory data include:

White blood cell count, 9600/ μ L

Hemoglobin, 14.2 g/dL

Hematocrit, 43%

Platelets, 300,000/ μ L

Neutrophils, 35%

Lymphocytes, 25%

Monocytes, 8%

Eosinophils, 12%

Basophils, 0%

What is the initial step in management?

- A. Discontinue carbamazepine.
- B. Begin intravenous vancomycin.
- C. Begin prednisone.
- D. Perform a skin biopsy.
- E. Begin intravenous immunoglobulin therapy (IVIG).

Answer: A This young woman is febrile, has eosinophilia, and has a rash that developed 6 weeks after starting carbamazepine. This clinical presentation is suggestive of drug rash with eosinophilia and systemic symptoms (DRESS). The next step in management is to remove the offending agent. Carbamazepine is a commonly reported medication that causes DRESS. Because the patient is febrile, an infectious etiology should be excluded. However, antibiotics are not indicated at this time. Systemic corticosteroids are recommended as part of the treatment of DRESS, but removal of the offending agent is crucial. In patients who do not respond to systemic steroids, IVIG can be

considered. Skin biopsy of these lesions shows perivascular lymphocytic infiltrate in the papillary dermis with eosinophils. Although a skin biopsy would be helpful in the diagnosis of DRESS, the first step should be to discontinue carbamazepine, since the clinical presentation is highly suggestive of DRESS.

Husain Z, Reddy BY, Schwart RA. DRESS syndrome: part II. Management and therapeutics. *J Am Acad Dermatol*. 2013;68:709-720.

3. A 34-year-old Asian woman presented to her primary care physician with dysuria and hematuria 2 weeks ago. She was treated with trimethoprim– sulfamethoxazole for 3 days for a urinary tract infection. She then presented to the emergency department this morning with fever, oral pain, and a rash. On physical examination, she has oral erosions with hemorrhage, as well as purpura on her lower extremities. With gentle pressure, she has sloughing of the skin. What is the next step in management?

- A. Provide supportive care.
- B. Begin vancomycin and piperacillin–tazobactam.
- C. Initiate intravenous immunoglobulin (IVIG) therapy.
- D. Begin infliximab.
- E. Begin corticosteroids.

Answer: A This young woman has clinical findings suggestive of Stevens- Johnson syndrome. Sloughing of the skin with gentle pressure is known as Nikolsky sign. The next step in management is supportive care, which includes transfer to a burn unit, fluid and electrolyte repletion, and ophthalmologic evaluation. She is at increased risk for bacterial superinfections, but antibiotics are not indicated for prevention of a secondary infection. The use of IVIG remains controversial, and randomized controlled trials have not been done yet. Tumor necrosis factor- α inhibitors, including infliximab, have been shown to decrease the time to reepithelialization, but starting infliximab would not be the next step in management. Corticosteroids have been frequently used as part of the management, but there no randomized controlled trials have evaluated corticosteroid use in Stevens-Johnson syndrome.

Worswick S, Cotliar J. Stevens-Johnson syndrome and toxic epidermal necrolysis: a review of treatment options. *Dermatol Ther*. 2011;24:207-218.

4. A 35-year-old woman noted a new onset of multiple pink papules that appeared suddenly and looked like mosquito bites. Three months later, most of these lesions had resolved, but new ones appeared. On examination, there are pink to red papules, some with ulceration and some with scarring. Biopsy of a papule shows a CD30+ lymphoproliferative disorder. All of the following are acceptable treatment options except:

- A. Oral low-dose methotrexate
- B. Systemic evaluation for lymphoma
- C. Multidrug chemotherapy
- D. Topical clobetasol
- E. None of the above

Answer: C These crops of pink papules that regress spontaneously are typical of lymphomatoid papulosis. Patients with lymphomatoid papulosis can also get mycosis fungoides or anaplastic large T-cell lymphoma. Oral low-dose methotrexate and topical corticosteroids, including clobetasol, are acceptable treatment options for lymphomatoid papulosis. Systemic evaluation for lymphoma should also be considered. It is important not to treat this patient too aggressively.

Duvic M. CD30+ Neoplasms of the skin. *Curr Hematol Malig Rep*. 2011;6:245-250.

5. A 56-year-old white man with well-controlled Crohn disease on oral mesalamine presents with an ulcer on his left lower extremity for the past 2 months. He denies any associated fevers or chills. Vital signs are blood pressure, 125/72 mm Hg; heart rate, 75 beats/min; respiratory rate, 14 beats/min; and temperature, 98.4° F. Physical examination reveals warm lower extremities with good hair growth, palpable distal pulses, and no edema bilaterally. Pinprick and vibratory sensation are intact on the plantar aspects of both feet. There is a deep ulcer with a violaceous border. Laboratory data include:

White blood cell, 7600/ μ L

Hemoglobin, 13.5 g/dL

Hematocrit, 46%

Platelets, 250,000/ μ L

Neutrophils, 57%

Lymphocytes, 37%

Monocytes, 5%

Eosinophils, 2%

Basophils, 0%

Hemoglobin A1c, 5.9%

What is the next step in management?

A. Débridement

B. Begin intravenous vancomycin therapy

C. Ankle-brachial index testing

D. Begin oral prednisone

E. All of the above

Answer: D The description of the ulcer and the patient's history of Crohn disease are suggestive of pyoderma gangrenosum. Oral prednisone is one of the initial therapies for pyoderma gangrenosum. A wound culture of the ulcer should be obtained to exclude an infectious etiology, but antibiotics are not indicated at this time. Débridement is contraindicated and can result in a larger wound. Because his pulses are palpable, ankle-brachial index testing is not indicated.

Ahronowitz I, Harp J, Shinkai K. Etiology and management of pyoderma gangrenosum: a comprehensive review. *Am J Clin Dermatol*. 2012;13: 191-211.

1. Acute lipodermatosclerosis is most commonly misdiagnosed as which of the following?

A. Allergic contact dermatitis

B. Irritant contact dermatitis

C. Cellulitis

D. A spider bite

E. Tinea pedis with extension on the ankle

Answer: C Acute lipodermatosclerosis is a form of panniculitis (inflammation of the subcutaneous fat) that manifests as tender, warm, erythematous plaques in patients with venous hypertension. The most common initial location is the lower extremity, superior to the medial malleolus. Because of its clinical presentation, acute lipodermatosclerosis is often misdiagnosed as cellulitis, but there is no fever or leukocytosis. Dermatitis has overlying scale-crust and is usually pruritic, whereas tinea has an active border with scale.

2. Disseminated gonococcal infection most commonly presents as tenosynovitis plus which of the following?

- A. Vesiculopustules on an erythematous base, scattered acrally
- B. Large areas of erythema studded with pustules on the trunk
- C. Retiform purpura with central necrosis on the distal extremities
- D. Morbilliform eruption on the trunk and extremities
- E. Multiple erythematous subcutaneous nodules on the shins

Answer: A The other descriptions are of (B) acute generalized exanthematous pustulosis, also referred to as a pustular drug eruption; (C) disseminated intravascular coagulation that can occur in the setting of several infections, including acute meningococcemia; (D) viral exanthem or the most common form of drug eruption; and (E) erythema nodosum.

3. Of the following entities, which is seen more commonly in African Americans than in Asians or Caucasians?

- A. Atopic dermatitis involving the antecubital and popliteal fossae
- B. Psoriasis of the elbows and knees
- C. Scabies infestation
- D. Pseudofolliculitis barbae
- E. Tinea (pityriasis) versicolor

Answer: D Entities that are seen more commonly in African Americans are outlined in Table 441-3.

4. A 60-year-old woman presents with an area of reticulated hyperpigmentation overlying the lumbosacral spine. She states that she has been suffering from chronic lower back pain. What is the most likely diagnosis?

- A. Dyskeratosis congenita
- B. Melasma
- C. Erythema ab igne
- D. Hyperpigmentation due to cupping and moxibustion
- E. Fixed drug eruption secondary to nonsteroidal anti-inflammatory drugs

Answer: C Erythema ab igne is seen at sites of repeated heat exposure, such as from heating pads and computer batteries. Hyperpigmentation due to cupping and moxibustion (traditional Chinese medicine) or a fixed drug eruption is circular in shape, not reticulated. Melasma can affect extrafacial sites, but they are primarily the extensor forearms and upper chest, and the lesions are circumscribed, not reticulated. Patients with the genodermatosis dyskeratosis congenita have reticulated pigmentation and pancytopenia, but lesions would not be limited to the lower back.

1. A 57-year-old woman complains of progressive hair loss involving the frontotemporal scalp and the eyebrows. She states that her hairline has been receding. Clinical examination shows a band of scarring alopecia on the frontotemporal scalp, as well as alopecia of the eyebrows. Perifollicular scaling is evident around the terminal follicles at the hairline, and dermoscopy shows perifollicular casts. A scalp biopsy shows loss of follicles and a perifollicular, lichenoid lymphocytic infiltrate with fibrosis. Which of the following is the *most* appropriate diagnosis?

- A. Traction alopecia
- B. Alopecia areata
- C. Androgenetic alopecia (female pattern hair loss)
- D. Frontal fibrosing alopecia
- E. Trichotillomania

Answer: D This patient has frontal fibrosing alopecia, which is a variant of lichen planopilaris and typically affects the frontal hairline of postmenopausal women with a bandlike scarring alopecia. It often is associated with marked decrease or complete loss of the eyebrows. Frontal fibrosing alopecia is a relatively newly defined condition that is becoming increasingly common worldwide. The cause of this condition is unknown. Possible treatments include intralesional or systemic steroids, systemic antimalarial agents, and excimer laser therapy.

2. An 18-year-old man complains of alopecia involving his entire scalp, eyelashes, and eyebrows since the age of 14. Family history is positive for a sister with type I diabetes. Dermoscopy shows yellow dots corresponding to empty follicular openings. Diagnosis of alopecia areata universalis is established. The patient is otherwise healthy and is seeking a rapidly effective treatment. Which of the following is the *most* appropriate treatment regimen?

- A. High-dose pulse corticosteroid therapy
- B. Intralesional steroid injections
- C. Clobetasol propionate cream 0.05% under occlusion
- D. Topical minoxidil 5% twice per day
- E. Topical immunotherapy with diphenylcyclopropenone

Answer: C High-dose pulse steroids are effective in patients with acute hair shedding but not in long-standing alopecia universalis, and intralesional steroids are an option only in circumscribed disease. Topical immunotherapy can be effective, but regrowth usually is not observed for 12 to 18 months. Topical minoxidil is not effective. The best choice for this patient is clobetasol propionate cream 0.05% under occlusion. Complete regrowth will be observed in 25% of patients with severe alopecia areata after 3 to 4 months of therapy.

3. A 32-year-old man complains of progressive thickening and yellow discoloration of his big toenails. Clinical examination shows dryness and desquamation of the plantar skin, subungual hyperkeratosis with onycholysis, and longitudinal yellow streaks of the first toenail bilaterally. Which of the following is the *most* appropriate recommendation?

- A. Start terbinafine 250 mg/day for 3 months
- B. Start terbinafine 250 mg/day for 6 weeks
- C. Take a nail clipping for KOH testing or culture
- D. Start itraconazole 200 mg/day for 3 months
- E. Start fluconazole 150 mg/week for 9 months

Answer: C The diagnosis of onychomycosis always requires laboratory confirmation. Numerous common nail diseases, including psoriasis and trauma, can appear very similar to onychomycosis on clinical examination. In this patient, culture isolated *T. rubrum*. Terbinafine 250 mg/day is started if laboratory testing confirms normal baseline liver enzymes.

4. A 64-year-old woman complains of progressive pigmentation of her left thumbnail over the past 2 years. Clinical examination shows a 5-mm large band of longitudinal melanonychia associated with pigmentation of the proximal nail fold. Which of the following is the *most* appropriate recommendation?

- A. Take a punch biopsy of the band
- B. Follow up after 6 months
- C. Take a nail clipping for pathologic examination
- D. Refer for a nail matrix biopsy
- E. Reassure her

Answer: D Longitudinal melanonychia with periungual pigmentation is highly suspicious for nail melanoma. Failure to diagnose nail melanoma can have fatal consequences for the patient. Diagnosis requires a nail matrix biopsy. A biopsy from the band is not appropriate for diagnosis because it will sample the nail bed, which is not the site of the tumor.

